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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

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3. Behrman, H. T., Combes, F. C., Bobroff, A., and Leviticus, R.: Ind. Med. & Surgery 18:512, 1949.
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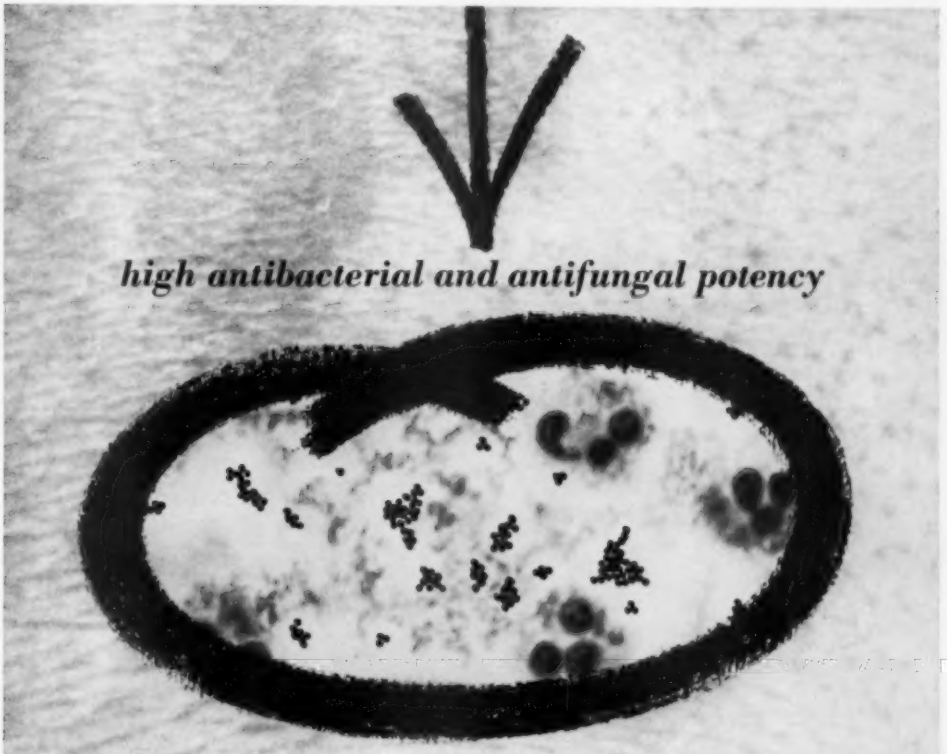

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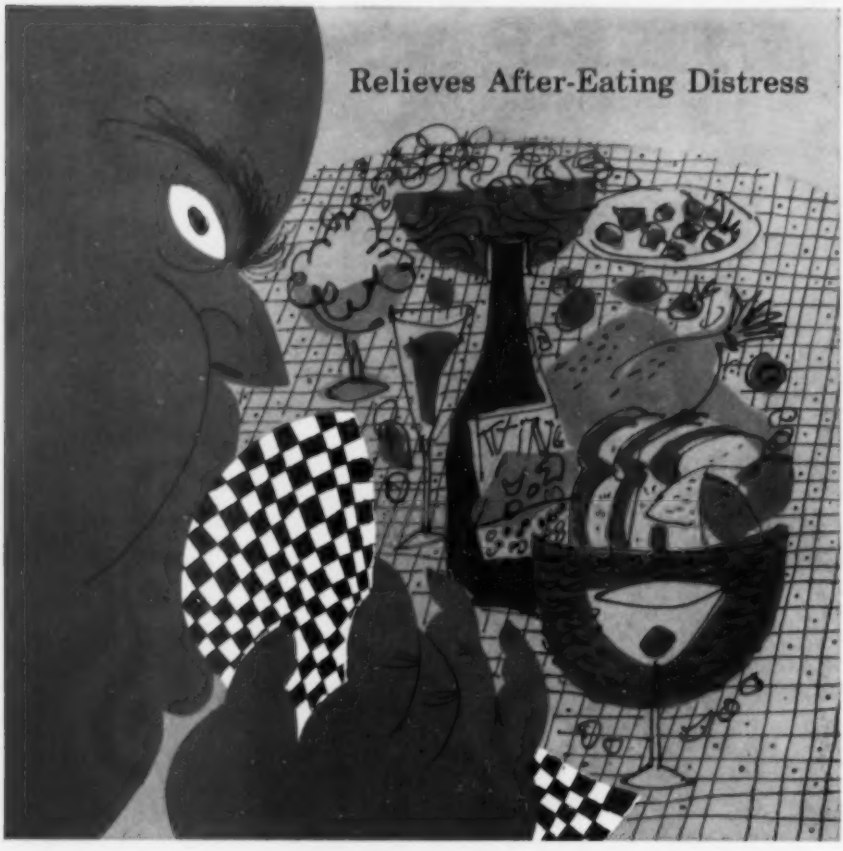

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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 31, NO. 6 JUNE 1955

PROBLEMS OF PROFESSIONAL MANPOWER*

"We Live Not As We Wish To But As We Can"

THE ANNIVERSARY DISCOURSE

FRANK B. BERRY, M.D.

Assistant Secretary of Defense (Health and Medical)

THE sub-title of this address, taken from a fragment of a poem written by the Greek poet Menander in the Fourth Century, B.C., is ever true. It has been impressed upon our generation since World War II, and even more so since the Korean conflict, as we try to correlate our resources with our aspirations for the present and the future. I entered college before World War I when all was seemingly at peace throughout the world. Because of the Spanish American War and the Boxer Rebellion and then our interest in arranging the Portsmouth Peace Treaty of the Russo-Japanese War, we had begun to spread beyond our own continental limits. The internal combustion engine was progressing at a 1910 pace and the airplane was still the plaything of a few hardy inventors; so we took rather comfortable courses in college with the philosophical and academic attitude of a purely educational experience as opposed to the training concept of the last quarter century. I

* Presented at the Annual Meeting of The New York Academy of Medicine, January 6, 1955. Manuscript received January 1955.

enjoyed one of these college courses particularly, little realizing at the time what a lasting impression it was to leave with me and how often I would turn back to it for refreshment and clarity of thought. This was a course in sociology given by Professor Thomas N. Carver. His one theme throughout the year was the question "What is progress?". It was asked of us on the first day of the course and again in May as we completed our work. During the year we studied and discussed at length the differences between progress and change and the differences in the effects on various periods of our civilization from new discoveries in geography, geology and the physical, chemical and biological sciences. Since that time the world has been in a state of turmoil almost continuously: with the First World War, Japan and China, Italy and Ethiopa, Spain, the Second World War, Korea and its sequelae. In addition there have been two major revolutions in political thought and economy, Russia and China, together with more orderly change in India, South Africa and elsewhere, so that now the same question as propounded for my study forty-three years ago becomes ever more acute.

Quite apart from wars and revolutions, what has happened to us in this intervening period? We have witnessed an extraordinary growth in industry as it then existed, and with the subsequent growth of many new industries, in medicine and in the physical and chemical sciences, there were always additions, never subtractions. With the rapid development of the automobile, particularly since World War II, there has come a complete change in our manner of living with dispersion into what was the distant country but now merely suburban areas. This has brought with it increased building of roads and houses and displacement and rearrangement of business. The whole airplane industry and its accessories has now become one of our major industries. The radio, television and electronics development are all products of the last thirty years, and since World War II we have witnessed an amazing growth in all fields of research: the chemical field, with tremendous development of plastics for example; the physical field with the fission and thermonuclear bombs and their problems not only of destruction but also of useful radioactivity and sources of power. These in turn have led into the field of geology with its intensified search not only for the metals and mineral and petroleum resources we have known in the past, but also a host of new minerals.

And finally we have medicine. At the time of World War I the so-called Golden Age of medicine was just drawing to a close. If the second half of the nineteenth and first two decades of the twentieth century were indeed this Golden Age, how shall we interpret the past thirty years with the incredible further development in all branches of medicine, inasmuch as medicine as it is taught today is scarcely recognizable to the medical student of forty years ago? Our annual mortality rate is now at an all time low, 9.5 per thousand, and life expectancy has been increased to 67.5 years. The reasons for this amazing progress in the field of medicine and preventive medicine are too well known to you for me to take the time to mention the many factors and steps that have contributed to it during this period.

Underlying this swift current of events, the basic source of its energy has been creative research with its ensuing development. In 1941 the total expenditures by government, industry and educational institutions for research and development were about eight hundred *million* dollars; in 1952 they were approximately three *billion* dollars. Thus, during this period the total expenditures for research and development increased 266 per cent, or allowing for inflation 95 per cent, and during this same period the gross national product increased only 44 per cent. Turning now to medical research alone, in 1941 the federal government contributed $185,000, whereas today it contributes fifty million dollars to the various medical schools in contracts and grants.

Throughout this brief recital of the march of events during the past generation, each must decide for himself what constitutes true progress and what mere change.

I have spent some time on this somewhat elaborate preamble in order to bring you to the decade of 1930-1940, the so-called depression years. During those years we had a very marked fall in the birthrate, yet at the same time our older age groups were increasing their longevity. For example, "In the mid 1940s about 100,000 males turned 18 each month. In 1952 only 90,000 males turned 18 each month. In the next three years there will be a slight gain with about 92,000 reaching this age each month. The number will rise to 97,000 in 1956 and will increase steadily through 1960." In other words, today we are not adding as many to our young, effective working population as we were in the mid 40s and will not approach that figure until 1957. During the decade from 1940 to 1950, on the other hand, the birthrate started to rise

TABLE I—LABOR FORCE: PER CENT

	1930	*1940*	*1950*
Professionals	6.1	6.5	7.5
Proprietors, etc.	19.9	17.8	16.3
Clerks	16.3	17.2	20.2
Skilled Workers	12.9	11.7	13.8
Semiskilled	16.4	21.0	22.4
Unskilled	14.1	14.4	19.8
Total United States Population		(132 million)	(152 million) (+ 15%)

rapidly so that at the present time we are faced with a temporary, real manpower shortage of young adults and we must therefore devise ways to make what we have stretch further. We have an increased population at both ends of life and a smaller group reaching the age of maturity. With the world situation what it is and our vast expansion in research and in industry, we must therefore calculate ways and means to utilize this middle group to the very best possible advantage.

Inasmuch as I am speaking as a representative of the Department of Defense, let us now consider the *military* manpower pool. This depends not only upon the number to be called up under the Selective Service System of those young men between the ages of 18 and 35, but to a certain extent on the number now in service who re-enlist, as these varying periods of enlistment and re-enlistment will affect the final number of men to be inducted.

To narrow the question still further, how does this concern medical education, the future hospital training programs throughout the nation and the needs of the Armed Forces? At the present time military medical requirements are met in the following manner:

First, each service notifies the Office of the Assistant Secretary of Defense (Health and Medical) of its needs during a given quarter of each year. These requirements are then verified and consolidated and the program is submitted to the National Health Resources Advisory Committee. They check our figures and also make investigations of their own, and then either approve or disapprove the data as submitted. If the former, a list of requirements is then submitted to the President

who personally approves the request, which is then finally transmitted to Selective Service, who makes the required call. The Office of the Assistant Secretary of Defense (Health and Medical) cannot interfere in any way with this call until a person who desires exemption has appealed through his channel of Selective Service Boards up to the National Health Resources Advisory Committee; then we may defer him for a period of six months only, which delay may, however, be renewed. We have *no* power of exemption.

At the present time we have about 220,000 physicians in the United States, an increase of almost 20,000 over those listed in 1950. That is our total supply. Of these, approximately 11,000 are retired and not in practice; 10,500 are in the armed services; and 25,000 are in training either as interns or residents. Incidentally, there are also 13,000 vacancies in intern and residency programs. Another factor of interest is that there are approximately 50,000 physicians under 51 years of age who have already served their required time in the armed services, some of whom are in residency training programs. Last year, for example, 6,861 students graduated from the medical schools, but of this number only about 2,900 at a maximum will be available for military service on the completion of their internship in June 1955, and the military needs are approximately 7,000 every two years, although with the new reduction in the Armed Forces this may be somewhat reduced. The armed services require many officers above the intern level. They need a certain number of more mature men with specialist training; therefore some means must be devised to produce these. Conversely, they cannot utilize a group made up entirely of men over 40, let us say, nor would it be fair to defer *all* the interns every year for completion of their residency training. In order to meet the needs of the future and to assure a smooth flow of doctors with varying degrees of training and skill entering the services, we believe, therefore, that the draft should be intelligently used so as to assure that a group of 1,000 to 1,200 interns each year may be deferred for further residency training. Such a deferral policy was recommended in 1952 by the National Manpower Council. Deferral does not mean exemption; hence, by this method none of this group will escape eventual service. If we refuse to disturb any of the older group now in practice, it is doubtful if we will ever be able to supply a sufficiently large group each year for deferral so as to maintain a smooth flow. In our opinion it is therefore necessary to utilize a draft

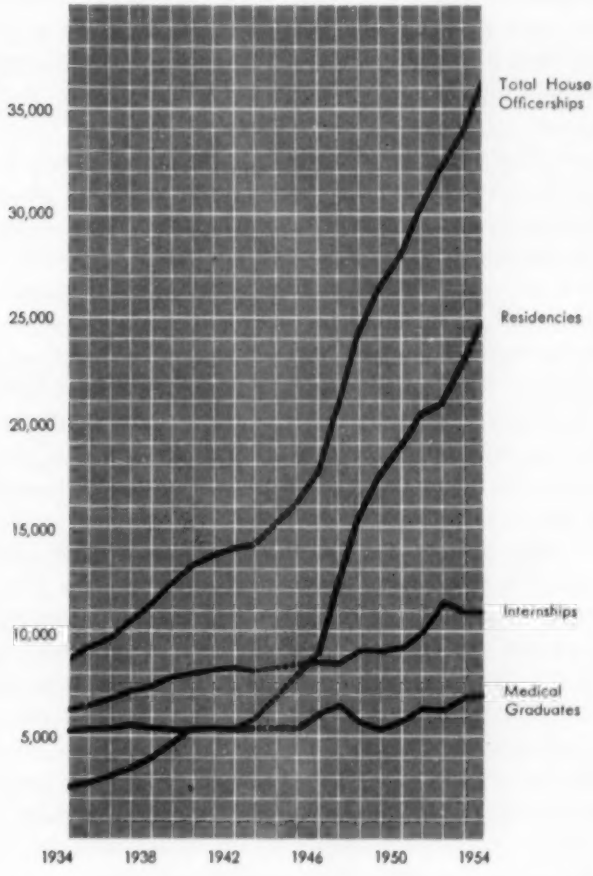
TABLE II—SCIENCE GRADUATES: 1950 AND 1954

	1950	*1954 (approximately)*
Engineering	52,000	17,000
Chemistry	10,500	6,300
Physics	3,400	2,100
Geology	3,000	1,900
All Others	40,000	24,000
(Medicine)	5,553	6,861

of older physicians in sufficient numbers so as to plan for the future and maintain a reserve in training to meet future needs. It seems to me that only by this method will we be able to attain a position where a "doctors' draft" is no longer needed. Two years will be required to get this deferral program well underway and provide an even supply of specialists and non-specialists. It is true that graduates from medical school each year are increasing. In 1940 there were 5,097; in 1950, 5,553; and in 1954, 6,861 as I have already mentioned. In the Class of 1955 there will probably be 60 per cent, about 4,100, who have never had military service, but in the year beginning July 1, 1956, when that class completes internship, 4,300 will be required for the military services; this leaves us no reserves. Furthermore, a few years hence medical school classes will contain men who have already served two years in the armed services under a regular draft status, hence the number of available medical graduates will then again decrease.

Let us explore the problem still further and in a somewhat more general sense. At the present time we have 38 million grade, high and college students and it is estimated that there will be 45 million in 1960. Half of those entering the fifth grade do not graduate from high school, and in turn one half entering college do not graduate. "The key to good education is good teaching. When able men and women are discouraged from entering upon a teaching career or leave after a few years because of low salaries and low prestige, it becomes extremely difficult for the nation to realize its educational goals." The same applies almost equally to medicine. At the present time able young men are discouraged from entering upon a medical career because the costs are

FIGURE 1



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so high and the course is so long. Dr. Alan Gregg has described a doctor's education as consisting of two parts: first, there are the twelve years in primary and secondary schools; then he faces another twelve years—college, medical school, internship, a residency of varying length and two years in the Armed Forces. With similar opportunities in research and in the allied biological, chemical and physical sciences, only

those hardy souls with a burning desire to study medicine will continue along this hard course. Others with allied interests and those who can be satisfied with paramedical work will take one of these paths, and after graduation from college, and perhaps with a master's degree or a doctorate, will find happy and productive lives in one of the allied sciences.

Just as in the case of the technocrats in the 1930s, so even now there are those who demand that their jobs be protected and governmental safeguards be provided so that unemployment may not increase. These seem to be needless fears because with our rapidly increasing population and our expanded research and development, the demands for new professions and skills are constantly being created. We do need planning along these lines, however, and we have the ever-present question of recruiting the right sort of men and women and in sufficient numbers for the medical profession, and for the nursing, public health and dental fields as well. There are now many positions in medical schools, particularly in the basic sciences, and also in our various state and governmental institutions, that cannot be filled. According to Dean Rappleye the quality of individuals going into medicine is not being maintained in relation to competition with other professions. The medical schools can not compete with our large industrial organizations in their drive for suitable recruits of good quality and, as you know, some are not able to fill their classes with well qualified students. Unfortunately, this is not widely recognized and the impression is still abroad that six or eight applicants are clamoring for each available place; as a matter of fact this has now decreased to approximately 2.5 per vacancy. We in the Department of Defense are equally interested in these questions and have already prepared legislation which would authorize the granting of scholarships to a total of 300 students per class in the medical schools throughout the country and a certain number in the dental schools. These scholarships will pay the entire tuition of the student plus a monthly allowance for his expenses. The aim here is twofold: first, we hope to gain about 300 physicians a year who would repay the scholarship on a year to year basis. The needs of the draft would thereby be lessened correspondingly. Second, we hope very much that some of those men who would like to go to medical school but who can not because of the expense burden, will apply for admission and might be accepted in their first year for such a scholarship. Another

method for increasing the attraction of medicine for well qualified students might be a re-appraisal of their requirements by the specialty boards. Most of these were organized and the rules formulated before World War II. Inasmuch as it seems likely that we shall maintain a large armed force for an unforeseeable number of years, possibly the Boards should review their policies so as to provide greater flexibility. The third method rests with the hospitals themselves. Many residencies were offered after World War II to provide training for those who had left the hospitals early in their career. With this need now satisfied there has still never been any reappraisal on the part of the hospitals, except in an upward direction.

Residency training has multiplied out of all proportion to internships. With the growth of our insurance plans and the increase in private, semiprivate and compensation patients in the hospitals the true opportunities for the full benefits of residency training have not by any means increased commensurately. As a matter of fact, as one talks with residents from various hospitals today it is generally and frankly admitted by them that they think their training could be shortened with no sacrifice in its quality, sometimes, as a matter of fact, even to advantage. In many instances there is too high a proportion of residents to patients with the result that a part of their service is spent in marking time. The duration of a residency, however, depends largely upon the rules laid down by that particular specialty board and the almost universal answer on the part of the intern or resident to the question "Why do you want this residency?" is "So as to satisfy the Board requirements." This is indeed a poor commentary on programs of education that should be devised and aimed at increasing the opportunity for the individual concerned for stimulation and increasing breadth of knowledge, and not just requirements for fulfilling a term measured only in time.

In the Armed Forces the ratio of doctors has now been reduced to 3.25 per thousand including those in the intern and residency programs, and of dentists, 2 per thousand. During the war the ratio of doctors was approximately 5 per thousand. I have now visited approximately fifty medical installations of all sizes of the Army, Navy and Air Force, including those in Europe, the United States, Alaska and the Far East. For the most part all of the doctors are busy and, provided the leadership is good, are generally happy in their work. I do not believe I have

noted any more overstaffing and idleness than one sees in a corresponding number of civilian institutions, if as much. Wherever I go I try to meet and interview the medical and dental officers and afford them full opportunity for questions. Their criticisms are both favorable and unfavorable with many of the questions purely on the neutral side and for information only so that the officer involved may better understand the problems at hand. As my acquaintance with the services increases it seems to me that they are just about at their lowest limits as regards medical and dental staffing. To cut deeper will endanger the quality of the work. This would be most unfortunate because the service rendered now is of extremely high order and in most instances well directed. Furthermore, the mere fact that there is troop reduction does not mean a corresponding drop in medical officer needs, because, due to the nature of the military organization, there are many commands and installations that still require medical staffing, quite exclusive of the hospital load *per se*. Were we faced only with the problem of hospitalization, it would be relatively simple to arrive at the most economical use of physicians and dentists. Far flung as our military installations are all over the world, however, with time consumed for travel, for training and for discharge, the whole operation must of necessity be wasteful to a certain extent. Military medicine does not consist entirely of work in hospitals. I speak for all the armed services, the Department of Defense and also for myself when I say that a certain training in the fundamental principles of military medicine, abbreviated though it may be, is of inestimable value. Had we not had a very small nucleus in Japan at the time of the Korean outbreak, our record would be far from what it is today. The threat still exists and we do not want to be caught again entirely unprepared in such a position. In order to prevent this, we must plan the best we are able not only for the present but for the future as well, so that all of us may share the burden equally as far as possible, and so that none of us will ever have to think to ourselves as did Richard the II in the closing lines of the play:

"I have wasted time, now doth time waste me."

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INTERACTIONS OF HOST, MICROBE AND CHEMOTHERAPEUTIC AGENT*

COLIN M. MACLEOD

Department of Microbiology, New York University College of Medicine

UNDER the very general title of this lecture it is proposed to discuss four aspects of the subject as follows:

1. The role of the nature of the lesion in the response to chemotherapy.
2. The nature of the drug: to include essentially a discussion of the terms "bacteriostatic" and "bactericidal" and their implications.
3. The role of immunity in recovery.
4. The development of resistance to antimicrobial drugs.

It is apparent that all four of these aspects are inter-related and one cannot be discussed without consideration of all of the others. The present purpose is to try to strike a balance among them and to show that although from a systematic point of view one can fracture the subject into these categories, yet in actual practice one can neglect none of them. The interplay is possibly best illustrated in infections caused by the tubercle bacillus and by staphylococcus in which the lesion is characteristically focal, where development of bacterial resistance is very common, where one cannot be sure that the bacteriostatic or bactericidal nature of the drug is of overriding importance, and where our gross lack of understanding of the immune processes leaves us with a foundation so insecure that we cannot interpret what has happened anyway.

One can go back to the sulfonamides and find that by 1939 many of the principles involved in scientific chemotherapy were quite well worked out and understood. With each new compound that has appeared since then the same principles have been found to be generally applicable although all too frequently the familiar lessons have had to be relearned. Enthusiasts report striking results that appear to contra-

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vene the basic principles. There follows a period of belief, progressively shorter with the skepticism that greets each succeeding compound, until the enthusiasts' claims have been independently tested and often found wanting. It should not be inferred from these remarks that nothing new has been found about the principles of chemotherapy since 1939 because that is not the impression one wishes to leave, but rather to emphasize that a good deal has been known for fifteen years and that this generally available information has not been so widely appreciated and applied as might be expected.

The Nature of the Lesion: It is a matter of common knowledge that the nature of the lesion, whether focal or diffuse, exerts an extraordinary influence upon the results of chemotherapy with any known antimicrobial agent. This became clearly apparent first in the treatment of pneumococcal pneumonia with sulfonamides. The diffuse pneumonic process as a rule was easily curable whereas focal lesions such as empyemata or abscesses were refractory even though the organisms present in these lesions were exquisitely sensitive to the drug. A number of factors were found to be important in the failure of sulfonamide therapy to influence the focal lesion: relative inability of the drug to penetrate into the lesion even though present in inhibitory concentrations in the blood, the presence in pus of inhibitors for the sulfonamides coupled with an unfavorable pH, absence of an adequate number of functional leukocytes, and a rich menstruum in which rapid growth of microorganisms could occur. In addition to these detriments there is the fundamental nature of sulfonamide action which is essentially bacteriostatic for most microorganisms both in vivo and in vitro, so that despite its presence, but in the absence of the normal body defenses, the bacteria are able to remain alive. Further, it was observed early in the study of sulfonamides that bacteria present in focal lesions are liable to become resistant to the drug, whereas this did not occur in diffuse lesions where the organisms were freely accessible to the drug and where the body defenses could collaborate unhampered. In order to circumvent the inability of the sulfonamides to diffuse from the blood into an empyema cavity, the compounds were injected directly into the pleural cavities, but without therapeutic success. This failure was due possibly to the nature of the drug—essentially bacteriostatic against pneumococcus—but probably more because of the variety of inhibitory factors present in the environment.

The earliest studies on penicillin indicated quite clearly that it does not suffer from certain of the disadvantages apparent in the sulfonamides. Penicillin was shown to have a rapid bactericidal action, albeit subtotal; it is not inhibited by body fluids whether normal or abnormal, and its antibacterial action is relatively independent of the number of bacteria present. Despite these extraordinary advantages, penicillin, when administered by intramuscular or intravenous injection, was entirely ineffective in the treatment of pneumococcal empyema. Failure was shortly shown to be due to the inability of the drug to enter *in sufficient amount* into the purulent pleural cavity, which is essentially walled-off from the general circulation, and as Tillett and his associates[1] showed in man, when penicillin is injected directly into the pleural cavity sterilization and healing usually occur. One does not know whether similar results would be found with the various tetracycline derivatives in pneumococcal empyema since they do not appear to have been systematically studied from this point of view. Such a study might reveal whether the most important consideration is the bactericidal activity or whether a bacteriostatic compound might also effect sterilization if its action were not nullified by various inhibitory factors as in the case of the sulfonamides.

Without doubt the nature of the lesion is the determining factor in the difficulties that confront us in the therapy of tuberculous and staphylococcus infections. In both cases the lesions are walled-off, relatively impermeable to the drug so that effective antimicrobial concentrations are hard to achieve within the focal lesions although extension may be limited, opportunity is given to the bacteria to develop drug resistance, and the task of sterilization within the walled-off areas remains largely the responsibility of the host.

Much has been made of the limitations of chemotherapy in infections where the organisms multiply intracellularly as in the case of the tubercle bacillus, the typhoid bacillus, the brucellae, the rickettsiae and the large and small viruses. We now know, however, that the site of multiplication, whether intracellular or extracellular, is not a prime determining factor, since effective chemotherapy is known for many microbes having an intracellular habitus. The gross nature of the lesion, i.e., whether it is focal as in the case of tuberculosis or non-focal as in typhoid fever or the rickettsial diseases, seems to be of much greater significance.

Nature of the Drug: Bacteriostatic or Bactericidal: The idea has grown up that modern chemotherapeutic agents belong to two very dissimilar biological classes: the bacteriostatic and the bactericidal. It should be recognized that these are quantitative terms and do not necessarily express qualitative differences. Moreover, what applies in vitro may not be found in vivo. The sulfonamides are commonly cited as prototypes of the bacteriostatic agents, and in the test tube this is true. It seems to be a splendid generalization also with respect to the in vivo action of the sulfonamides, but there is at least one striking and medically important exception. And it is exceptions of this sort that make one pause in making broad generalizations about the in vivo action of a drug based on the little world of the test tube. The exception in the case of the sulfonamides is their action upon meningococci in the human pharynx. Early studies in chemotherapy of meningococcal meningitis showed that shortly following the use of sulfonamides in treatment there occurs a total disappearance of meningococci from their normal habitat—the nasopharynx. Subsequently it was shown through studies in Navy and Army establishments early in World War II that a modest dosage of sulfonamide given for a day or two is effective in permanently ridding the nasopharynx of meningococci.[2] Under these circumstances the sulfonamides act like the most dramatic bactericidal drugs, yet we cannot so class them from in vitro studies which have shown them to be bacteriostatic. The participation of the host is obviously of crucial importance in this bactericidal effect in vivo and should cause us to have the greatest reserve in generalizing from in vitro results. Unfortunately we know next to nothing about the factors in the host that normally exert an antimeningococcal action and which act in concert with the sulfonamides to give a bactericidal effect, so that no interpretation can be given of the action of the sulfonamides in vivo in this case except in the most general terms.

We have observed similar, apparently bactericidal effects with tetracycline derivatives in experimental chemotherapy of mice with pneumococcal infections.[3] These compounds are commonly classified as bacteriostatic. The application of this epithet is based on their action in the test tube and also upon observations in naturally occurring infectious diseases of man such as the rickettsioses where it is apparent that the tetracyclines require the generous participation of the host factors in order to exert a permanent cure. However, when Aureomycin for

example, is used to treat pneumococcal infections of mice, in our experience it acts bactericidally—in fact it mimics closely the action of penicillin and is strikingly different from the sulfonamides even though both the tetracyclines and the sulfonamides are generally put together in the category of bacteriostatic agents.

The real difficulty may lie in the use of words and the general conceptions which they invoke. Thus the terms bacteriostatic and bactericidal have somehow acquired the halo of biological absolutes when in point of fact they do not express qualitative differences except under narrowly defined in vitro conditions. If one wished to set up a theoretical scheme based on in vitro tests he might place the sulfonamides at the extreme left as bacteriostatic agents and over at the far right place penicillin as a bactericidal agent. Between these extremes might be ranged the other antibiotics, most of which are considered to be essentially bacteriostatic because of their action in the test tube and the occurrence of relapses in certain diseases of man unless they are employed for relatively protracted periods or under conditions of dosage so that the development of immunity can occur without undue delay. Such a scheme can look very pretty and be a satisfying device in didactic teaching, but actually it is not so clarifying a concept as it is generally considered to be. Experience has taught us, both in natural and experimental infections, that one cannot rely on it as a guide to the therapeutic regimen in a particular disease. Even with the paradigm of bactericidal agents—penicillin—one does not dare to use the hit and run approach of a single dose in even the most susceptible infections in man because we know that one can rarely get away with it. A large residue of organisms remains alive. Contrariwise, the classical examples of bacteriostatic drugs, the sulfonamides, exert in meningococcal infections as striking a bactericidal effect as can be found in the whole field of chemotherapy.

The moral that may be drawn from this brief discussion of bactericidy versus bacteriostasis is that while the discrimination between these effects is superficially satisfying, it really provides no consistent guide to what one can expect when antimicrobials are used in the treatment of disease. Host factors that we know something about and others that we know next to nothing about, so modify the events in the complex milieu of the infected host that each compound must be reassessed in each disease even though results in the test tube may have indicated

a general pattern of activity which might be expected to apply in experimentally infected animals and in man.

The Role of Immunity in the Curative Action of Antimicrobials: Early in our studies of the action of sulfonamides in the late '30's the great importance of the specific immune response in recovery of mice experimentally infected with pneumococci became apparent.[4, 5] It was found that treatment had to be continued for two or three days if recovery was to be expected. This period coincided exactly with that required by normal mice to develop specific immunity upon injection of heat-killed pneumococcal suspensions. Moreover, the results varied with pneumococci of different types depending on their antigenicity. For instance types 1 and 2 are excellent antigens in the mouse. Sulfonamide treatment for three days of mice infected with these types gives recovery rates close to 100 per cent and the survivors are found to be solidly immune. On the other hand, comparable amounts of heat-killed vaccines of type 3 are very poorly antigenic in the mouse, and even with optimal sulfonamide treatment of type 3 infected mice, survival occurs in less than 10 per cent. The effect in the case of type 3 is so poor in comparison to that seen with types 1 or 2, that if sulfapyridine had been tested only against type 3 infections in mice it might never have been employed in general chemotherapy of pneumococcal infections.

With penicillin the role of immunity in the recovery of mice from experimental infections was by no means so clear cut. Indeed, immune processes seemed to play little part under the conditions of our experiments which involved infection with relatively small numbers of organisms and prompt treatment.[5] It looked as though penicillin had approached Ehrlich's dream of *Therapia magna sterilisans*—at least in the mouse under these experimental conditions. These findings did not apply in the treatment of patients with pneumonia, however, as was shown by Tillett and his associates.[6] They found that treatment must be continued if a good therapeutic effect is to be achieved. After a single dose of penicillin the clinical picture may improve remarkably, temperature falls, the patient becomes more comfortable, but the cure is short-lived because within eighteen to twenty-four hours the disease commonly recurs in full severity. What is the reason for this great difference between the experimental infection in mice and the natural disease in man?

It seems possible that the number of organisms present in the host

may have a good deal to do with the differences observed. In the mouse an inoculum of 10,000 organisms was used in our experiments. The killing action of penicillin, which is on the order of 99.9 per cent, thus leaves only a few bacteria, and these, though still living are not multiplying and can be disposed of by the host's defenses. A different situation pertains in the human disease where the number of organisms present in the involved lung is measurable in billions rather than the paltry thousands we employed in our mouse experiments. The bacterial count may well be 10^{10} organisms or higher at start of therapy. If 99.9 per cent are killed this still leaves a large number (10^7) for the host defenses to handle, and with excretion of the drug these living organisms can multiply rapidly and symptoms recur unless specific immunity has developed, or some other defense mechanism such as phagocytosis in the absence of antibody is now effective.

Even with the prototype of bactericidal drugs, penicillin, therefore, the immune response appears to be of crucial importance, and probably because the killing action of the drug is subtotal.

In the therapy of a number of other diseases of man with antibiotics, the immune response has also been shown to exert a decisive influence. It is relatively easy to induce a remission of symptoms of typhoid fever, scrub typhus or tularemia by means of chloramphenicol, for instance. However, relapses are very frequent unless treatment is started relatively late in the disease, presumably by the time the antigenic mass has grown sufficiently large, though this is supposition. If treated early it has been observed that relapse will occur in typhoid about fifteen days after treatment is stopped, in rickettsial diseases six to eight days after therapy is discontinued, and in tularemia four to six days following withdrawal of the drug.[7] It so happens that in all of these infections the site of multiplication of the agent is intracellular. It is not true from the chemotherapeutic point of view, however, that the site of multiplication is the consideration that sets these diseases apart from those in which microbial multiplication is extracellular, because as has been found in the case of pneumococcal pneumonia, the specific immune processes also play a crucial role. It is hazardous, however, to attempt to generalize from pneumococcal infections to typhoid, rickettsioses or tularemia. In pneumococcal infections the important antigen has been identified, it is produced in large amounts by the bacteria and the immune response to it is prompt provided the antigen is present in sufficient amount—

which seems to be the case in the usual infection. With the other infections mentioned we do not know what antigen or antigens are important, nor under what circumstances they are liberated from the bacteria in order to give immunity. It seems likely, however, that they are present in very small amount, or that they are weakly antigenic, or that the antibodies produced for some reason or another act in a very inefficient fashion.

A general summary of the role of the immune response indicates clearly its great importance in effecting cure even in the presence of compounds which have a marked bactericidal effect. It is also plain that until we know a good deal more about the immunology of a number of diseases such as typhoid, tularemia, brucellosis, and the rickettsioses, our chemotherapy is on an unsound, trial-and-error basis. It is to be hoped that the delight in juggling drug dosage schedules will not blind our scientific curiosity to the important questions to be answered if therapy of these diseases is to be put on a rational basis.

The Development of Resistance to Antimicrobial Drugs: Most of you are aware that this is a very old problem and that it antedates the modern miracle age. Ehrlich encountered it in his studies of ortho-quinoid dyes as antispirochetal agents and it was also noted by him for arsenicals. It was observed by Morgenroth in his investigations on the action of optochin on pneumococcus. Likewise it has been a bugaboo in the use of various antimalarials and more recently with insecticides. Much of the mystery has been removed from drug resistance by the realization of the "adaptability" of microorganisms to inimical environments through the emergence of mutants that are able to survive under conditions totally unsuited to the generality of the species. The keys to this understanding are the size of microbial populations and the frequency of mutations of a particular sort.

In a single generation of microorganisms mutation rates occur on the order of 1 to 10^6 to 1 to 10^9 organisms. That is to say that 1 out of every million or 1 out of every billion organisms has mutated so that its constitution may permit it to survive in an environment unsatisfactory for the rest of the population. This may appear to be so small a fraction of the total number that it is of little or no consequence. One must bear in mind, however, the size of microbial populations. One milliliter of a fully grown broth culture of most species of bacteria contains from 200,000,000 to one billion organisms. The number present

in the host at a given time may be a large multiple of this figure so that the size of the population can easily be great enough to make it likely that a sufficient number of mutants will appear so that a significant number can survive unless other factors such as specific body defenses can be brought into play to cope with them.

In some infections the appearance of resistant mutants is an uncommon and unimportant event and does not constitute a limitation of therapy. For example, penicillin-resistant pneumococci or Group A streptococci are unknown in clinical practice despite the general use of this substance. On the other hand the use of sulfonamides in treatment of Group A streptococcal infections during World War II was all but nullified by the appearance of sulfonamide-resistant organisms following the widespread use of these compounds for prophylaxis.[8] Similarly the therapy of staphylococcal and tuberculous infections is bedevilled by the appearance of mutants resistant to the drugs that can be used.

In each of these instances the nature of the lesion exerts a large effect, although the mutational capacity of the microbe and the properties of the antimicrobial also play a significant part.

Shortly after the introduction of the sulfonamides into clinical practice it was observed that pneumococci became resistant to them both in vitro and in vivo, and that the resistant microorganisms bred true whether the drug was present in the environment or not.[9] As noted earlier it was also observed that the nature of the lesion is important since pneumococci in the semi-isolated world of an empyema were liable to become resistant whereas this was not encountered in diffuse, drug-available lesions such as a pneumonic process in the lung. The combined action of a therapeutic concentration of drug in the infected lung plus the uninhibited action of highly effective body defenses sufficed to prevent the emergence of resistant mutants, whereas the sequestered empyema, low in sulfonamide and with various inhibitory factors, permitted resistant mutants to flourish. It was observed early that in order to develop a high degree of resistance it is necessary as a rule to expose bacteria to gradually increasing concentrations of a particular compound. Demerec[10] formalized this in his studies on resistance of staphylococcus to penicillin. In general terms, the transition from susceptibility to complete resistance involves a number of mutational steps. A mutant that is resistant to a low concentration of drug survives and

grows out whereas the susceptibles in the population die or are killed. The next step in resistance is taken when the mutant that has just emerged and survived the lowest drug concentration has grown out to a population size large enough so that a second, even more resistant mutant has a chance to appear. Subsequently, increasingly resistant mutants appear in the same stepwise fashion, although in the case of streptomycin, resistance may develop through single successive mutational steps or in a single step.

It can be seen that low concentrations of drug applied to large numbers of organisms over a long period of time afford the best opportunities for progression up the stairway to resistance. Moreover, if there is a gradation of concentrations of drug, as can easily be visualized in different parts or zones of the focal lesions of tuberculosis or staphylococcal infections, the selection of mutants having higher degrees of resistance becomes possible.

Resistance to more than one antimicrobial has become a commonplace of clinical chemotherapy. If the drugs have different modes of action the emergence of resistance to both of them in the same bacterium involves separate and distinct mutations. The chances of two mutations of this sort occurring at the same time in the same bacterial cell are very much less than a single mutation to resistance to only one of them. For example, if mutation to the first step of resistance to penicillin occurs at a rate of 1 to 10^7 and to Aureomycin at the same rate, then the chance of both occurring in the same cell at the same time is the product of the two rates, or 1 to 10^{14}. For this reason it seems probable that bacteria which show dual resistance have usually acquired one first and then the other, rather than both mutations occurring at the same time in the same cell. This is the basis for using two compounds simultaneously rather than using one first and then following with the other at a time when resistance to the first has already appeared. Employment of two drugs at the same time is no guarantee, however, that dual resistance will be prevented because the two compounds may not always or perhaps even often be present in all of the lesions in equivalent antibacterial concentration. That is to say that even though the two compounds are administered at the same time their distribution in the lesions may be so unequal that the bacteria can first develop resistance to one drug and subsequently to the other. Nonetheless, it should be remembered that the chances of developing resistance are distinctly less when

compounds are used at the same time.

The combined use of drugs is justified, however, only in conditions where one knows that resistance is likely to develop such as in focal lesions. There is rarely an excuse for the use of multiple drugs in diffuse, non-focal lesions where the occurrence of resistant variants is rare. All too often, it would seem that the concept is "If one drug is good, two are better," forgetting the dangers of sensitization of the patient to the compounds and drug toxicity. For these same reasons it is unfortunate that antimicrobial drugs are used so indiscriminately in the treatment of minor maladies such as the common, non-bacterial respiratory infections, where a therapeutic effect has never been shown.

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EVALUATION OF PENTOTHAL®† ANESTHESIA AFTER TWENTY YEARS—ITS USE AND ABUSE*

VINCENT J. COLLINS

Department of Anesthesiology, St. Vincent's Hospital, New York, N. Y.

IN the year 1933, Lundy and Tovell[1] began the clinical use of thiopental sodium. Since then this drug has attained preeminence in popularity. A host of reports have appeared covering the use of thiopental in major surgery, abdominal and chest, in dental practice and in office practice, in head and neck surgery without endotracheal airway. It is as if the handbook of nomenclature of operations was used and prefixed by the words, "Intravenous Pentothal for . . .". McQuillen[2] analyzed the literature from 1935 through 1946. There were 574 references to barbiturates. Unquestionably, the only requirement to administer sodium thiopental is to be able to get a needle into a vein. Not until the disasters at Pearl Harbor was there any general questioning of the safety of the drug.[3] In the skepticism of this apparent anesthetic panacea investigation naturally returned to the original work by Lundy and Tovell.

It is a curious fact that pioneers in any field of endeavor often either instinctively or intuitively, find the correct ways of performance and then enunciate their intuitive know-how as guides. Lundy was a pioneer in the clinical use of thiopental and his principles regarding its use have stood the test of time and experience and have been substantiated experimentally.

These principles deserve to be stated again and again: 1) Simple operations; 2) Short duration (about one hour); 3) Dosage limit of 1 gram. As soon as the anesthetist deviates, the hazards are increased out of proportion to the inescapable hazard normally presented by the nonconforming case.

The intent is not to belabor clinical experience but to review a few

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† Pentothal Sodium—brand of thiopental sodium, Abbott Laboratories.

outstanding examples of experimental observations regarding the physiologic and pharmacologic effect of thiopental. It is such as these that lend insight into the proper application of our tool.

As a preliminary it seems necessary to make one plea—a plea for physiologic anesthesia. This does not necessarily mean smooth anesthesia, nor should smooth anesthesia be the only goal in administering an anesthetic. The goal should be maintenance of a good physiologic state. However, too often anesthetists have been desirous of making things appear good and in doing so have compromised body function. Many surgeons have fostered this attitude and in some clinics it has become routine to induce anesthesia in all patients with intravenous thiopental. Anesthetists have in many instances sacrificed principles for expediency. This is both an abuse of the drug and an abuse of our patients. Recently a very prominent anesthesiologist announced that all cardiac patients should be put to sleep with thiopental, in order to avoid any excitement. This indicates a failure to individualize cardiac conditions and a lack of pharmacologic knowledge of the drug. Bishop[4] has stated that a little excitement is not per se a bad thing and an attempt to prevent excitement too often depresses the patient, lowers the blood pressure and limits compensatory responses. In other words smooth anesthesia is often attained at the price of good physiology. The gist of this plea is not criticism but a desire to see more anesthetists develop their ability to administer an inhalation anesthetic. By this I mean carrying out an induction with an inhalant that is rapid and smooth and physiologic! To do this one must become an expert at talking a patient to sleep; to calm him with suggestions and in a sense to develop powers of hypnosis. A preoperative visit with the patient is mandatory, and postoperative observation is essential. This is the psychology of anesthesia.

Oximetry has shown the profound effect of even small doses of sodium thiopental on arterial oxygen saturation.[5] The first important contribution along this line was by McClure, Behrmann and Hartman[6] at the Henry Ford Hospital. They showed that with the administration of as little as 10 cc. of 2½ per cent thiopental the blood oxygen saturation would fall rapidly to values below 60 per cent. They demonstrated that supplementary oxygen in high concentrations is of definite advantage, not only during maintenance of anesthesia with thiopental but during the induction period, no matter how brief this might be. They concluded that it is important to reach maximum oxygenation at the begin-

ning of the anesthetic since it was easier to maintain a good level of oxygenation than to bring it about after a period of decreased oxygen saturation. Further details of their work demonstrated that only as long as oxygen in concentrations above 40 per cent were administered to a patient under thiopental would the arterial oxygen saturation remain at 90 per cent or better. They further showed that if thiopental is administered for two or more hours to a patient that thereafter oxygen saturation tends to decrease even if concentrations of 100 per cent oxygen are breathed. In general other workers have substantiated these findings.

In 1948 studies were done on "The Effect of Pentothal Sodium on Blood Gas Transport."[7] It was shown that two particular effects occurred rather quickly after the administration of a single dose of thiopental. One of these was hemodilution and the other, of which we are all aware, was depressed ventilation. These two factors accounted to a large extent for the lowered oxygen capacity that was found. However, it was suggested that to account completely for the lowered oxygen capacity observed, thiopental perhaps interfered intrinsically with the combination of oxygen and hemoglobin.

Significant to the study of shock has been the work of Shorr and his co-workers,[8] on the peripheral-vascular system. The various mechanisms needed to maintain circulatory balance have been investigated. It has been shown that the peripheral circulation[9] is anatomically divided into (a) the larger vessels, acting as conduits for distribution of blood to organs and body regions and (b) the small vessels or capillary unit which supply oxygenated blood in accordance with oxygen needs to the tissue and cells of the body. Of importance in regard to the larger vessels is the mechanism of vasoconstriction, a property possessed by arterioles. In regard to the smaller vessels it was shown that they are not only a definite anatomical unit but an important functional unit as well. This capillary unit consists of ramifications of terminal arterioles called muscular capillaries which are then further subdivided into nonmuscular or true capillaries. This capillary bed is denoted by a marked responsiveness to circulating drugs as well as to metabolites of tissue origin and normally shows intermittent changes of activity called vasomotion. The reactions of this capillary unit when subjected to blood loss are characteristic and predictable when under the influence of anesthetic drugs.

With thiopental anesthesia the pattern of response during periods of stress such as surgery is initially fairly good.[10] Later however, deterio-

ration of the mechanism of vascular response occurs. Vasomotion fails, the capillary bed becomes dilated, stasis develops with congestion and extravasation of red cells. Throughout this period, however, vasoconstriction is good and in the experimental animal, even persists until death. This seems to indicate that the effect of thiopental on the central neurogenic mechanism of vascular control is little changed but that the all important peripheral capillary unit rapidly falls.

Furthermore, Shorr[8] has demonstrated that during periods of stress, vaso-active principles appear in the blood stream. These may be either of an excitatory or a depressor type. The first is of kidney origin; the second of liver origin. In reference to the vaso-excitor material or V.E.M. all compensatory responses are usually in good order as long as it is appearing in the blood stream. However, when the vaso-depressor material begins to appear there is a loss in compensatory ability. When the organism is under the influence of thiopental, V.E.M. is present initially, but is gradually replaced and completely so finally, by the depressor material.

Some quantitative pharmacologic studies have also been carried out with respect to the distribution and metabolism of thiopental. Mark and Brodie[11] have shown that when a given dose of thiopental is injected into the human being and blood tissue levels subsequently determined, there is a characteristic pattern to the concentrations of the thiopental. Initially, there is a rapid reduction in plasma levels but instead of the thiopental concentration falling to zero, there is a tapering off of the curve. Actually the early plasma decline represents a distribution of the thiopental with the establishment of a plasma-tissue equilibrium. There is tissue localization and this results in a tissue reservoir from which the blood stream continues to receive small amounts during the so-called postanesthetic interval. The tissues actually involved are the body fats and hence thiopental takes its place along with most of the other anesthetic drugs in showing a definite affinity for lipoid substance. Substantiating this work in part are the results obtained using radioactive thiopental with the isotope sulfur 35 incorporated in the thiopental molecule.[12] An even distribution of thiopental in body tissues occurs within thirty seconds of the injection. Very little remains in the blood stream. Subsequently there is a slow decline in the amount of thiopental in the tissues.

As long as two hours after a single half-gram injection of thiopental a plasma level of about 3 mg./liter is detectable. Also of interest is the

fact that the thiopental concentrations in most organ tissues were definitely higher than in plasma. About 80 per cent of the circulating thiopental was found to be bound presumably by surface absorption to plasma protein. It has also been shown, that although thiopental is almost completely transformed in the body, the rate of this transformation in man is quite slow being approximately 15 per cent per hour. Two transformation products have been isolated, which account for about 30 per cent of the parent drug. One of the metabolites is an oxidation compound in which one of the thiopental side chains is changed to carboxylic acid and has identical ultraviolet properties with the parent drug thiopental but has little anesthetic activity.

Some observations on blood pressure changes accompanying the administration of sodium thiopental are of significance.[13] It is well known that the rapid administration of highly concentrated thiopental solutions produces sudden apnea but also causes rather marked circulatory depression with precipitous blood pressure drops. In 100 consecutive unselected cases 0.2 per cent thiopental was administered by the drip technique, taking an average six to eight minutes to produce unconsciousness. During this time readings of the blood pressure were made every half minute. All cases were well premedicated (not depressed) and calm with pulse rates 80 per minute or below. Invariably there was a blood pressure drop varying from 12 to 50 per cent within the induction period. Only in adult patients between ages of twenty to fifty years in good condition were the blood pressure falls minimal but they still occurred, and were definitely out of all proportion to what would be expected with the assumption of the state of sleep. In the older patients with blood pressures in range between 120 and 140 mm. Hg, the blood pressure drops average 22 mm. of mercury in systolic pressure. In patients with hypertension and pressures between 150 and 200, pressure falls of as much as 80 mm. of mercury systolic occurred. Emphasis should be placed on the fact that thiopental was administered to these patients slowly and the concentration used was dilute. Nevertheless, a severe stress was placed on the circulatory systems of all the patients investigated.

Corroborative clinical evidence of hypotension occurring as the result of administration of thiopental has been reported.[14] It is particularly noted following the rapid "shot gun" techniques. As pointed out by Stephen, hypotension following thiopental will be observed "if the

physician is watching for it."

With respect to the cardiac mechanism, it is considered that the ultra short-acting barbiturates have a direct weakening effect on the myocardium.[15] Furthermore, Etsten[16] has observed a 10 per cent fall in cardiac output with sedative doses of thiopental alone. Doses capable of producing first plane levels of anesthesia reduce cardiac output about 25 per cent.

These observations are of tremendous importance particularly when one is administering thiopental to cardiac patients and more specifically to those with coronary artery and anginal disease. It is these patients who suffer from falls in pressure since it is peripheral blood pressure, particularly the diastolic pressure upon which the coronary circulation is dependent and when there is a fall in arterial pressure, coronary artery flow falls concomitantly.

What may practical anesthetists and surgeons draw from these observations? The conclusions are inescapable!

Thiopental should not be used for prolonged surgical procedures. Besides being impotent as regards achieving deep surgical anesthesia it also depresses cardiovascular responses important in allaying shock. At the same time thiopental allows the accumulation of material with a vascular depressing action, and should not be given to poor risks or the patient who is a candidate for shock.

Thiopental is not the ultra short-acting barbiturate it was once supposed to be. A tissue reservoir is established early and for as long as six to fourteen hours tends to feed into the plasma stream a small amount of thiopental. This is the reason for frequent cases of drowsiness, stupor and depression seen after thiopental anesthesia especially in the elderly patient and helps explain the pulmonary complications frequently seen. In fact as one continues to administer thiopental it takes on more of the characteristics of pentobarbital.

In brief, some anesthetists in two decades have swung back, they have returned to Lundy's principles. This most useful of anesthetic agents can now be seen in proper perspective and can assume its proper place in anesthesiology.

Thiopental is indeed an excellent tool if handled properly. Of course, most everyone has used it in the situations considered to be the physiologic and pharmacologic contraindications and has not been aware of many great or frequent disasters. But in dealing with the human organ-

ism we can "get away with an awful lot." This circumstance does not give anyone license to continue a bad practice. There are definite indications for the use of thiopental; its use should be individualized. If thiopental is considered more as a basal narcotic – an intravenous one at that – rather than as a pure and complete anesthetic agent, the anesthetist will be able to extract maximum benefits with minimal complications. A de-emphasis of thiopental is warranted. It is only one of many anesthetic drugs in the competent anesthesiologist's armamentarium.

I wish to thank the members of the Section on Surgery, and particularly, Dr. Moore, your secretary, for the kind invitation for us who are working in anesthesia to meet with those men with whom we are so closely associated. I believe it is a reflection of that accord given to physician-anesthetists which one of your illustrious and recently deceased members was so wont to emphasize. I would like to quote one of Dr. Frank Lahey's statements made in 1935:

"It is being realized more and more clearly that the anesthetist should not be subservient to the surgeon but should cooperate with him so that the special knowledge of each is used most effectively. Division of responsibility comes in the realization of each man of the limitations of his own knowledge and allowing the man with the proper knowledge and technical know-how to solve the problem presented as best he can." It is needless to point out to progressive surgeons, that our mutual cooperation has one aim, namely, the welfare of the patient. It is increasingly clear that the anesthesiologist's role is that of the internist in the operating room. He deals with aspects of clinical physiology and pharmacology, while the surgeon devotes his time and energies to surgical problems and concentrates his skill in the restoration of anatomical continuity. Such a definition of activities on a mutual cooperation basis can lead to but one thing: better patient care.

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RENAL FUNCTION DURING GENERAL ANESTHESIA*

E. M. PAPPER

Director, Anesthesiology Service, Presbyterian Hospital, New York

THE establishment of general anesthesia produces widespread circulatory and metabolic adjustments which are presumably calculated to preserve the integrity of the blood pressure and the perfusion of vital tissues. Associated with these changes are derangements in the composition and distribution of body fluids.[1, 2] The quantitative definition of all of these alterations is far from complete. Of assistance in the understanding of some of these has been the acquisition of knowledge of renal function during general anesthesia.

Most of the information on kidney function has been obtained in connection with its role as a circulatory organ and its effects on the excretion of water and electrolytes. Much less information is available on the influence of acidosis or anoxia during anesthesia and even less is known about the mechanisms which produce the kidney changes that have been defined.

It is the purpose of this discussion to present some of the patterns of renal functional change during general anesthesia and to attempt to make some appropriate interpretations of their significance.

Early studies by Coller and his associates[3] showed that there was no essential change in glomerular filtration or renal plasma flow in man during ether anesthesia. They observed a depression of glomerular filtration with a less definite effect upon renal plasma flow with cyclopropane. In general, it was concluded that these two agents had a relatively small influence upon glomerular filtration and renal plasma flow. These conclusions have not been confirmed by others but it seems probable that the explanation for the discrepancies lies in the time at which measurements were made. Measurements were made by Coller et al. before anesthesia and after the conclusion of operation. It is possible in

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From the Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, New York.

this manner to miss the changes in renal function during anesthesia. Recovery from alterations of glomerular filtration and renal plasma flow occurs toward the end of operation or shortly thereafter.[4]

Among the many variables that influence the observations on renal function are those of depth of anesthesia. Craig, Visscher, and Houck[5] found in the dog, that light anesthesia with ether or cyclopropane produced no significant effects upon glomerular filtration and tubular function. However, during deep anesthesia these functions were reduced approximately 50 per cent. These workers concluded that the effects were due to afferent renal arteriolar constriction on a neurogenic basis. At this point, it is necessary to point out that in none of the published studies was there quantitative determination of the depth of anesthesia, either by the measurement of arterial blood levels of the anesthetic agent or by electroencephalographic control. Since depth of anesthesia apparently has important influences upon renal function it must be kept in mind that some of the differences of opinion may be based upon the fact that depth of anesthesia is either unknown or inadequately measured by clinical signs.

In 1949, Burnett and his co-workers[6] studied the influence of ether and cyclopropane on renal function in unoperated man. The depth of anesthesia was "light or moderate". No premedication was used. Ether anesthesia produced a depression of glomerular filtration averaging 21 per cent which tended to improve as anesthesia progressed. Renal plasma flow was decreased an average of 39 per cent with a rise in filtration fraction of 25 per cent. The urine flow decreased 51 per cent because of increased reabsorption of water as well as a decrease in glomerular filtration and renal plasma flow. These investigators observed greater changes in renal function during cyclopropane anesthesia. The glomerular filtration fell an average of 31 per cent. Renal plasma flow was reduced an average of 52 per cent and the filtration fraction rose an average of 35 per cent. Burnett et al. concluded that the influence of these two anesthetic agents in depressing glomerular filtration and renal plasma flow was clear and definite but the effect of cyclopropane was greater than that of ether. These conclusions were confirmed by Habif et al.[7] under somewhat different circumstances. The changes observed by Habif and his associates were greater than those of Burnett et al. Qualitatively they were in the same direction and it is possible that the greater alterations observed by Habif et al. were due either to

dehydration of their patients or perhaps to greater depths of anesthesia. Habif et al. made no attempt to hydrate patients whereas Burnett and his associates attempted adequate hydration prior to study. Breed and Baxter[8] emphasized the great importance of the variability of dehydration and starvation preoperatively in terms of influence upon renal function.

The influence of the barbiturates on renal function is not as well known as those of the inhalant anesthetic agents. In the dog, Corcoran and Page[9] found that pentobarbital does not affect glomerular filtration or renal plasma flow in doses of 30 mg. per kilogram given intraperitoneally. Glauser and Selkurt[10] concluded that sodium barbital and pentobarbital have little or no influence upon glomerular filtration in the dog during a period of five to six hours. There was, however, a diminution of renal plasma flow during the same interval. This effect was not thought to be significant. In fact, Glauser and Selkurt concluded that the barbiturates were perfectly satisfactory for employment in animals where renal function was to be studied. Thiopental, in man, produces effects similar to those of cyclopropane and ether.[7]

It has been well known that morphine, among the premedicant drugs, produces a fall in urine flow.[11] However, it appeared important to define the influence of at least several of the common premedicant drugs upon discrete renal functions in a quantitative manner. Accordingly, Habif and his associates[7] studied the influence of meperidine and morphine in full therapeutic doses on man. They found that glomerular filtration decreased from 21 per cent to 45 per cent and renal plasma flow decreased 24 per cent to 50 per cent. The urine flow was diminished particularly during a water diuresis. During the diminution in urine flow there was an increased concentration of sodium, potassium, and chloride in the urine but the diminution in water output was so great proportionately that the total electrolyte excretion was actually diminished. The effect of 10 mg. of morphine was somewhat less marked than the effect of 100 mg. of meperidine. Atropine in doses of 0.5 mg. had no apparent influence upon renal function. No studies were made of the effect of scopolamine.

Interpretation

It appears from the information available that anesthetic agents that produce loss of consciousness have a profound, more or less uniform,

and nonspecific effect upon renal hemodynamics and urine formation. The hemodynamic changes that are observed in the kidney are those of intense intrarenal vasoconstriction which persists no longer than the period of unconsciousness. The arteriolar constriction appears to be both afferent and efferent as evidenced by reduction in both glomerular filtration and renal plasma flow. The magnitude of reduction in blood flow through the kidney is great and when taken together with the simultaneous reduction in flow through the splanchnic circulation it is evident that there is a reduction in peripheral blood flow through these two major organ systems of approximately 50 per cent. There must, therefore, be a considerable redistribution of blood flow during anesthesia. Its exact pattern and its meaning remain for future study. These changes are certainly not due to the trauma of operation in the absence of shock and hemorrhage since identical influences are observed during anesthesia without operation and, in fact, the alterations in renal function tend slowly to be restored toward normal even in the face of operation. It does not appear that these changes, i.e., renal vasoconstriction, reduced glomerular filtration, and water and electrolyte retention are mediated through the autonomic nervous system. It was observed by Berne and Levy,[12] for example, that, in the dog, when cardiac output was reduced acutely by pulmonary artery constriction the changes in renal blood flow, glomerular filtration, and sodium excretion were not different in innervated and surgically denervated kidneys. In man, in the fragmentary evidence available, it seems probable that high spinal anesthesia does not alter the renal responses to general anesthesia, provided that there is no important change in blood pressure.[13] Furthermore, Miles and his associates[14] were unable to observe changes in renal hemodynamics and glomerular filtration during cyclopropane anesthesia after the administration of methonium compounds.

It is unlikely that the effects upon renal function during general anesthesia are directly due to a drug effect since they are rapidly reversible after the termination of anesthesia during the period when the concentrations of the anesthetic agents in body tissues could not have been altered significantly.[15, 16] It is most striking and perhaps of great importance that the hemodynamic changes observed during general anesthesia in the kidney resemble those seen during shock, congestive heart failure, severe pain, chronic anemia, severe exercise, or sudden change in posture. These situations, including general anesthesia, pos-

sibly have in common the fact that visceral vasoconstriction serves the purpose of diverting blood temporarily from organs where it is not immediately needed to other areas of the body such as the heart and the brain that are quite sensitive to oxygen deficits.

These interpretations, of course, cast no light on the mechanism of the production of these disturbances. It is possible that the hemodynamic changes are due to an humoral agent which appears quickly in the circulating blood after the establishment of general anesthesia and clears as rapidly on recovery. For example, the intravenous infusion of epinephrine and norepinephrine produces renal function changes which are strikingly similar to those caused by general anesthesia.[17]

The disturbances in urine formation and electrolyte secretion can be attributed only in part to the release of antidiuretic hormone by the posterior pituitary gland. The diminution in electrolyte excretion during general anesthesia is significant and is not accounted for by diminution in plasma concentration of sodium, potassium or chloride. It is more likely that the fall in glomerular filtration resulting from intrarenal vasoconstriction permits a relative increase in the tubular reabsorption of both electrolytes and water. General anesthetic agents do not account for the failure of the kidneys to make appropriate adjustments in the immediate postoperative period since these functions have been returned to normal prior to this period. It is possible, however, that the tubules have been conditioned in some way by anesthesia and operation so that excretion of water and salt loads in subsequent days is inefficient. Possibly oversecretion of adrenal cortical hormones and cellular changes in renal tubules consequent to prolonged vasoconstriction may have some part in this problem. Measurements made by Ariel and Miller[18] suggest that renal plasma flow is essentially normal in the postoperative period and, in fact, glomerular filtration is actually increased moderately. Moyer[19] believed that the postoperative derangements of urine formation and electrolyte control are due to shifts in body fluids in response to stimuli of a painful nature from the operative area.

A possible explanation of the changes occurring in electrolyte excretion, particularly of sodium, is concerned with the effects of peripheral venous congestion. Alterations in venous pressure and venous congestion are not unusual during anesthesia. Their cause is not always clear but these effects may follow small increases in resistance to breathing and minor and unrecognized degrees of obstruction to breathing. It has

been shown by Frieden and his co-workers[20] that the dog kidney will retain abnormal amounts of sodium due to increased tubular reabsorption during induced peripheral venous congestion. Furthermore, this mechanism in the kidney is not necessarily accompanied by a fall in glomerular filtration or renal plasma flow. These changes also occur with generalized elevations of venous pressure and not necessarily confined to the renal venous circulation.

Unfortunately there are no data available on the effects of anoxia during general anesthesia in man. In unanesthetized animals and human subjects, Axelrod and Pitts[21] found no significant effects upon renal tubular function or glomerular filtration during moderate anoxia induced by the inhalation of gas mixtures low in oxygen. Selkurt,[22] however, demonstrated in dogs anesthetized with pentobarbital, that hyperemia in the kidney could be produced by anoxia together with an increase in the excretion of sodium, potassium and water. Concomitant measurements of the effect of increased tensions of carbon dioxide during these experiments were not made.

Summary and Conclusions

General anesthesia appears to produce a stereotyped response in the kidney dependent in part upon the depth of anesthesia and in no way dependent upon the specific anesthetic agent used. The greater the depth of anesthesia the more profound the changes. These changes consist of a striking intrarenal vasoconstriction associated with a fall in glomerular filtration and a reduction in the excretion of electrolytes and water. There is a relative increase in tubular reabsorption of both electrolytes and water. These changes are extensive and are similar to those seen in other alterations of physiological activity or in a variety of diseased states which may be considered stressful. In the absence of shock and hemorrhage, surgical operation has little influence on these renal functional changes. The precise mechanism of these alterations in kidney function is not known. It appears possible, however, that these alterations are due to an humoral effect, possibly from the adrenal medulla or the adrenal cortex. The striking renal dysfunction which may occur in the postoperative period is not due to the influence of the anesthetic agent but presumably to other factors involving the responses to stimuli from the operative area with subsequent shifts in body fluids.

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NEW YORK PATHOLOGICAL SOCIETY

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ENDOCARDIAL FIBROELASTOSIS: OLD AND NEW CONCEPTS*

PAUL D. ROSAHN

THE purpose of this report is to present a descriptive synopsis of endocardial fibroelastosis, touching on its historical, clinical and morphologic aspects, and surveying present concepts on its etiology and pathogenesis. To this end, the findings on four personally observed cases will be utilized, and in addition reference will be made to the available literature, with especial emphasis on publications which have appeared since 1950. Evidence will also be presented which suggests that the disease is associated with generalized vascular changes, and that it is genetically determined.

The best recent definition of endocardial fibroelastosis is perhaps that given by Gowing:[1] "Fibroelastosis of the endocardium is a congenital condition of unknown etiology in which there occurs a diffuse thickening of the mural endocardium associated in most cases with myocardial hypertrophy, and leading to early death." Historically, fibrous thickening of the endocardium with or without valvular deformity or other congenital cardiac abnormalities has been believed to be the end-result of inflammatory changes occurring in the endocardium during the gestation period, i.e., of fetal endocarditis. Indeed, throughout the last century, and also in the early decades of the present century, fetal endocarditis was accepted as an important factor in the production of cardiac developmental defects in general. Only a few dissident voices opposing this concept were raised, until the major contribution

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of Paul Gross[2] in 1941. Gross reviewed the historical background of the fetal endocarditis theory, and its presumed role in the production of fibrous thickening of the endocardium. From him we learn that Pototschnig[3] in 1918 was the first to suggest that endocardial thickening and sclerosis is the result of a simple, non-inflammatory hyperplasia of fibroelastic tissue. Gross presented the findings on a personally observed case of a full-term newborn boy with stenosis of the mitral and aortic valves, in whom there were also hypoplasia of the root of the aorta, rudimentary development of the left ventricular cavity, a large patent ductus arteriosus, an anatomically patent but functionally closed foramen ovale, and diffuse parietal endocardial sclerosis of the left ventricle. In Gross' opinion, these lesions were non-inflammatory because of the histologic absence of inflammatory residua. He also concluded that the occurrence of fetal endocarditis has never been established. Weinberg and Himelfarb[4] in 1943 were the first to use the term "endocardial fibroelastosis" although before and since their report many other designations for the abnormality have been employed, in addition to "fetal endocarditis." These include subacute infective endocarditis, elastic tissue hyperplasia of endocardium, fetal endomyocarditis, endocardial sclerosis, endocardial fibrosis, and idiopathic cardiac hypertrophy. Since 1950 the appellation "endocardial fibroelastosis" appears to have been generally accepted for, of thirty publications[1, 5-33] on the subject, twenty-two have employed this term, "endocardial sclerosis" having been used six times, and "endocardial fibrosis" and "fetal endocarditis" once each.

Cases which on review appear to be instances of endocardial fibroelastosis have been reported not only under the designation "fetal endocarditis" but also as "congenital idiopathic hypertrophy of the heart." Thus Kugel and Stoloff[34] in 1933 reported on seven cases of this condition, six of these seven showing mural endocardial thickening due to fibroelastic tissue. The case of Powers and LeCompte[35] also revealed fibroelastic thickening of the endocardium lining the left auricle and ventricle. At present it appears that congenital idiopathic hypertrophy of the heart embraces two different patterns, namely glycogen storage (von Gierke's disease) involving the myocardium, and endocardial fibroelastosis.

Two types of cardiac lesions have been excluded from the present discussion because there exists some doubt concerning their nature.

The first of these is the African disease kwashiorkor.[36] This is a malady occurring in children, and characterized by hypoproteinemia, anasarca, liver fibrosis and degenerative myocardial changes. Ultimately endocardial fibrosis, especially in the left ventricle, may develop. The disease probably results from a nutritional deficiency. The second type of cardiac lesion which will not be considered here, occurs in young adults, and has been reported in West African soldiers, and elsewhere.[37] There is enlargement and dilatation of the heart, focal myocardial fibrosis, and fibrous thickening of the endocardium. Death is said to result from congestive heart failure. The cause has been ascribed to many factors, but a definitive etiology is not yet known.

Case Report

The clinical and anatomical findings in endocardial fibroelastosis are well illustrated by a case that came under recent observation.

B.M., a five months old white girl, was born at the New Britain General Hospital. Her mother, a primipara, age nineteen, was Rh (D) negative, but sensitization did not occur during pregnancy which in all respects was uneventful. Delivery was spontaneous at term, the child weighing 6 pounds. No abnormalities were noted at birth. Subsequent growth and development were normal. At two months of age the child developed a severe bronchiolitis for which she was hospitalized. Following treatment with antibiotics she was discharged on the fifth hospital day. Two weeks prior to her present admission she became ill again and was brought to her physician. On this examination the pediatrician noted a rapid respiratory rate, but the chest was clear and resonant, and the heart sounds were normal. On the evening before admission the child had a nasal discharge, with cough, irritability and grunting, rapid respirations. On admission she was listless, irritable, with rapid shallow respirations, and cyanosis of the lips and extremities. There was a mucoid nasal discharge, and moderate injection of the pharynx. The chest was resonant and clear, but breath sounds over the left base were decreased. The heart did not appear to be enlarged to percussion, the rhythm was regular and there were no murmurs. The abdomen was entirely negative. On admission the temperature was 98°F. The child was placed on antibiotics and oxygen. On the afternoon of admission the temperature rose sharply to 105°F., respirations became labored and grunting, and marked cyanosis developed. She was pronounced dead fifteen minutes after the onset of the acute episode.

At autopsy (No. 52-87), in addition to the principal findings which were in the heart, there was pulmonary congestion and edema, and a patchy exudate involving the lower lobe of the right lung. The liver was not congested. The heart weighed 105 grams (normal 30 grams) and was markedly enlarged to the left. The parietal and visceral layers of pericardium were not remarkable. The left ventricle was hypertrophied and markedly dilated forming a nearly spherical cavity. As a result of this dilatation, the interventricular septum bulged into the right ventricular cavity. The endocardium of the left ventricle was uniformly thickened and porcelain-white. The trabeculae carneae and

the papillary muscles were flattened and the spaces between them appeared as depressions which were also lined by thickened endocardium. The left atrium likewise had a lining of thickened pearly white endocardium, but the right side of the heart did not show this change. None of the valves was abnormal. The ductus arteriosus was closed. The foramen ovale was covered by a membranous flap which could be pushed aside with a probe. The coronary arteries arose from the aorta in the usual manner. The diameter of the aorta was not notably reduced.

Microscopic examination of the heart revealed the characteristic changes which have been described and illustrated by many observers. These will be discussed more extensively in a subsequent section of this report, but they will be briefly summarized here. The changes included hypertrophy of the myocardial fibers, absence of inflammatory infiltrates, and marked thickening of the involved endocardium by elastic and collagen tissue deposits.

Frequency

The frequency of occurrence of endocardial fibroelastosis is difficult to estimate. In our first ten years' experience at the New Britain General Hospital 205 autopsies were conducted on subjects under two years of age, and only two instances of the disease were noted. In the subsequent three years ending July 1, 1953, an additional sixty-four infants under two years were examined at autopsy, and in this group were two more cases. In the first series of 205 autopsies the frequency of the disease was less than 1 per cent, while the second series of sixty-four autopsies revealed a frequency of about 3 per cent among autopsies on individuals under two years of age. Lambert et al.[22] observed 2352 consecutive autopsies on infants and children between 1935 and 1942. In this group there were fifty-four instances of death resulting from heart disease. The most frequent gross congenital anomaly was complete transposition of the great vessels which was seen in twenty cases. The second most frequent abnormality was mural endocardial fibrosis which occurred in fifteen cases. The precise frequency of fibroelastosis of the endocardium may never be satisfactorily determined, but it is fair to say that this condition is one of the most frequent of congenital cardiac anomalies.

Sex and Racial Distribution

Dennis et al.[8] in 1953 collected the largest number of cases from the literature, a total of 149. Others also have collected and reported on large groups of cases. Lambert et al.[22] in 1953 discussed fifteen cases of their own and added seventy-nine cases from the literature. Gowing[1] in the same year collected seventy-six cases including three of his own. Blumberg and Lyon[6] in 1952 described twenty-five personally observed

cases, and analyzed these, together with sixty-nine additional cases from the literature. Adams and Katz[5] in 1952 discussed twenty-one cases of their own among which four were still alive. In the same year Johnson[18] analyzed twenty-three cases culled from 210 congenitally malformed hearts which he had observed. Most of the cases so reported and collected, and others reported in smaller groups are without question true cases of endocardial fibroelastosis. But a few of the reports on individual cases are so sketchy, or so poorly documented, that their acceptability is in doubt. This is true especially of some of the instances of endocardial fibroelastosis diagnosed in children over three years of age. Nevertheless, even with these reservations in mind, both sexes are approximately equally affected. In Dennis' collected series,[8] for example, of the 143 cases in which the sex was stated, 53 per cent were male and 47 per cent were female. The disease has been observed not only in white children, but in Negroes also, and case reports have described endocardial fibroelastosis in an American Indian[22] and in a full-blooded Indian[21] born in the Arctic region.

Clinical Findings and Course

The most frequent clinical finding in the case reports reviewed is respiratory difficulty which includes statements of dyspnea, orthopnea, grunting, wheezing, crowing, etc. Although cyanosis occurs, it is of interest that this is usually not present initially. Cyanosis is either entirely absent, or intermittent or terminal in about three-quarters of the cases. Cardiac murmurs are either absent or are described as distant and faint, also in about three-quarters of the cases. An enlarged heart on chest roentgenogram is an almost constant finding. Other symptoms, occurring less frequently, are: difficulty in feeding; anorexia; failure to gain weight; irritability; vomiting; tachycardia; and evidence of right heart failure. Most of the cases have palpable pulsations of the femoral arteries, and many have E.C.G. evidence of left ventricular hypertrophy in the precordial leads. The laboratory findings are usually non-contributory.

The clinical course of this disease may be conveniently divided into two distinct types. The first is an acute form. The patient is a young infant, usually under six months old, who may have had an episode or two of irritability, anorexia or cough, but whose health has in general been good. The child is suddenly taken with dyspnea, cough, vomiting, cyanosis and tachycardia. The heart is enlarged, and usually there are

no murmurs or thrills. The child's condition deteriorates steadily and death occurs within two weeks. A variant of the acute type occurs in the infant, previously well, who has a sudden explosive attack of dyspnea and cyanosis, and dies within minutes or hours. Indeed, any discussion of sudden death in infants must include endocardial fibroelastosis as a leading cause.

The second form that the disease may take is chronic in type. The onset and symptoms are similar to the acute form, but the infant recovers. There are remissions and exacerbations, with episodes of right heart failure and ultimately death. In not more than about 15 per cent of all cases does the disease last for more than six months.

No specific treatment has yet been devised, and so far as is known the disease is invariably fatal.

Age at Death: The age at death of patients with endocardial fibroelastosis is best summarized by the tabulations of Dennis and his associates,[8] based on 149 collected cases. The disease has been observed in two stillborn babies, one of which had an estimated age of eight lunar months.[29] This suggests that whatever the pathogenesis may be, it can be operative during early fetal existence. About three-fifths of the reported cases were under six months of age at the time of death, and four-fifths were under one year. At least some of the cases reported in children dying at age one year to eleven and one-half years are suspect, but nevertheless even in this age group the characteristic findings of endocardial fibroelastosis do occur. Fifteen per cent of Dennis' series died at age one to three years, and 6 per cent died between the ages of three and eleven and a half years.

Of the ninety-four cases reported by Lambert et al.,[22] none of which had coarctation of the aorta, anomalies of the coronary arteries, or other gross cardiac abnormalities, 92 per cent died at age one year or less. None of the eight cases observed by Prior and Wyatt[29] and none of the four cases at the New Britain General Hospital, survived one year of age. These data clearly emphasize that the disease occurs predominantly in infants under one year of age, and more especially in the age group under six months.

Anatomic Changes

Gross Findings: An examination of the case reports of endocardial fibroelastosis discloses three general types of gross anatomic findings.

Cardiac hypertrophy in terms of heart weight is a constant occurrence. In all cases endocardial fibroelastosis occurs in one or more chambers, and except in rare instances, the sclerosis involves the endocardium of the left ventricle. The left atrial endocardium is next most frequently involved. Less than half of the cases show involvement of the right ventricle, and only a small group reveals thickening of the endocardium of the right atrium. Usually the entire left side of the heart shows the lesion, and only infrequently are one, or three, or four chambers affected. The involved endocardium is diffusely thickened, smooth and porcelain-white. The trabeculae carneae are flattened and sometimes completely effaced. In rare cases adherent mural thrombi have been noted.

In addition to the endocardial changes, about half of all cases, and in some series even less than half, show thickening, sclerosis and deformity of one or more valves. In this group with valve changes, the mitral and aortic valves in combination are most frequently involved. Next most frequently involved are the aortic valve alone, and the mitral valve alone. Only rarely have changes been seen in the tricuspid or pulmonic valves. Emphasis should here be placed on the fact that at least half and perhaps more than half of all cases show only endocardial thickening, with no disturbance in the integrity of the valves.

Still a third group presents other cardiac anomalies, in addition to the endocardial changes. Those reported include coarctation of the aorta, anomalous origin of the left coronary artery, partial transposition of the great vessels, patent ductus arteriosus, patent foramen ovale, or bicuspid aortic valve, singly or in combination. These anomalies occur in about 10 to 15 per cent of all cases, and usually but not invariably are accompanied by thickening, sclerosis and distortion of one or more valves.

Microscopic Findings: Tissues from the four personally observed cases were prepared for histologic study after staining with hematoxylin and eosin, and by Verhoeff's elastic tissue and Masson's trichrome stains. The marked thickening of the involved endocardium which was observed on gross examination was readily verified on microscopic study (Figs. 1-4). The endocardial ground substance was increased in amount, and scattered through it were elongated fibroblastic nuclei. Lymphocytes and indicators of inflammation were absent. The distribution of elastic tissue in the thickened endocardium was characteristic and uniform in

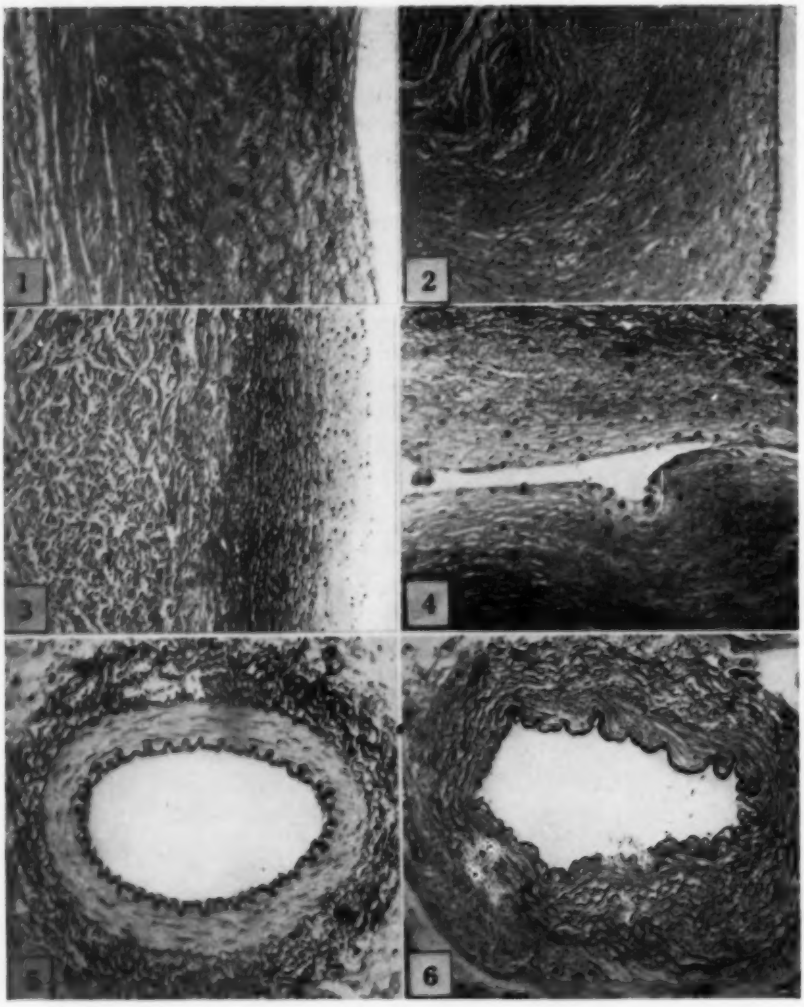

Fig. 1—Autopsy #50-39. Fibroelastosis of endocardium. Male, six months old. Masson trichrome stain showing thickened endocardium. X140.

Fig. 2—Autopsy #45-32. Fibroelastosis of endocardium. Female, three months old. Hematoxylin and eosin stain showing thickened endocardium. X140.

Fig. 3—Autopsy #52-87. Fibroelastosis of endocardium. Female, five months old. Verhoeff elastic tissue stain showing thickened endocardium. X160.

Fig. 4—Autopsy #45-32. Verhoeff elastic tissue stain showing thickened endocardium. X225.

Fig. 5—Autopsy #50-39. Verhoeff elastic tissue stain showing hyperelastosis of mesenteric artery. X300.

Fig. 6—Autopsy #50-39. Verhoeff elastic tissue stain showing hyperelastosis of coronary artery. X170.

(All photographs were prepared by Mr. Howard J. Reynolds)

all sections from all hearts. At the junction with the subendocardial tissue, the elastic fibers were compactly grouped in dense masses. The individual fibers were arranged in long sweeping, sometimes intermingling, slender threads, but occasionally they occurred in fragmented thicker, stubby forms. The number and density of the elastic fibers gradually decreased as the lumen of the cardiac chamber was approached, with the result that elastic fibers were generally absent in the subendothelial portions of the endocardium. Occasionally elastic fibers were found in the loose tissue between the myocardium and the endocardium, but this was not a striking feature. The distribution of connective tissue as revealed in trichrome stained preparations generally paralleled that of the elastic tissue. Concentrations of connective tissue were observed close to the myocardium; far less collagen occurred subendothelially. Conspicuously present in those areas which were devoid of both collagen and elastic tissue, that is, beneath the endocardium, were swelling, edema, and a basophilic ground substance with few nuclei, resulting in an overall myxomatous appearance.

Stellate cells with small nuclei, distinct cell boundaries and an absence of cytoplasm were occasionally noted in a contiguous bead-like arrangement in the loose subendocardial tissue. These had the appearance of Purkinje cells. In general the myocardium and the epicardium were not altered. None of these hearts showed necrosis, calcification, inflammation, fatty infiltration or an increase in glycogen, although all of these changes have been reported in affected hearts. Occasionally collagen fibers swept down from the endocardium, through the loose subendocardial connective tissue to the subjacent myocardium, but significant fibrous scarring of the myocardium was absent.

Constant and specific changes (Fig. 6) were noted in the medium-sized and small branches of the coronary arteries located within both the subepicardial tissue and the myocardium. Kugel and Stoloff[34] in their 1933 report on idiopathic cardiac hypertrophy described and illustrated these changes in two hearts, both of which fulfill present criteria for a diagnosis of endocardial fibroelastosis. Each of the four hearts in the present series showed changes similar to those noted by Kugel and Stoloff, namely, a marked periarterial, adventitial hyperelastosis. Endothelial alterations and thrombi were absent in the affected vessels, which also showed no evidence of inflammation. The increase in elastic tissue mimicked the findings in the involved endocardium, and

occurred outside of the external elastic membrane of the vessels. These changes were not observed in all coronary vessels in all sections, but were revealed in multiple sections of all four hearts. For this reason it is concluded that the perivascular hyperelastosis is segmental and spotty in distribution, and does not occur uniformly along the entire course of the artery.

The observation of hyperelastosis of the coronary arteries in affected hearts suggested the probability that similar changes might occur in other vessels. Accordingly elastic tissue stained sections from other organs were studied. Adventitial perivascular hyperelastosis and fibrosis (Fig. 5) were found in medium-sized and small arteries of the parenchymatous organs of all four cases. The organs involved were lung, pancreas, kidney, spleen, adrenal, intestine, uterus and thymus. Again, these changes were spotty—not all sections of all organs from each case showed them, but they were present in all cases. On comparison with control tissue of non-affected individuals, the elastosis was found to be quantitatively greater in the endocardial fibroelastosis cases, but not qualitatively different.

Theories of Etiology and Pathogenesis

Any discussion of the etiology and pathogenesis of endocardial fibroelastosis must unfortunately in this stage of our knowledge be replete with theory and hypothesis, and deficient in fact and demonstrated proof. Several theories have been advanced, and these will be described here. Most of them have attempted to explain the "how" of endocardial fibroelastosis, rather than the "why."

Fetal Endocarditis: As indicated previously, the early thinking about this problem postulated that in utero inflammation of the heart, that is fetal endocarditis, is responsible not only for the endocardial changes, but occasionally also for other cardiac anomalies. This concept, which was fully explored by Gross, has been based largely on the presence of histologic changes interpreted by various observers as the end-results of an inflammatory process. These changes include necrosis and calcification in the myocardium, connective tissue scars, dilated capillaries, vacuolization, fatty change and occasional cellular infiltrates in the myocardium. These, however, need not necessarily be the result of an inflammatory process, but rather may be indicative of a degenerative phenomenon. Valvular lesions were also believed by some to be evidence

of in utero inflammation, but histologic study of such valves has shown them to be uniformly devoid of active inflammation. A hurdle which the proponents of the endocarditis theory have never surmounted is the fact that the acute phase of fetal endocarditis has never been demonstrated, for all cases described are in the so-called healed, inactive stage. Since Gross' carefully reasoned and documented report, the theory of fetal endocarditis has steadily lost ground, and now apparently has been completely discarded.

Maternal Infection: Maternal infection during pregnancy has been reported, but such occurrences are uncommon rather than the rule. Influenza, la grippe, rhinitis, infectious mononucleosis, upper respiratory infections, vaginal bleeding, and rubella during the pregnancy which terminated in a child who developed endocardial fibroelastosis, have all been described. It is difficult to evaluate these findings. The great majority of case reports do not contain detailed accounts of the mother's health during her pregnancy. Moreover, to be of value, such infections and disturbances must be shown to be more frequent in the mothers of affected children than in the general population of mothers. Because of the infrequent occurrence of endocardial fibroelastosis, a difference of this type is hardly likely ever to be demonstrable.

Mechanical Factors: A majority of the deaths from endocardial fibroelastosis result from heart failure, usually left-sided failure. Several suggestions have been offered to explain heart failure in this disease. Weinberg and Himelfarb,[4] and others, postulate that the fibroelastic thickening of the endocardium interferes with the emptying of the arterioluminal vessels by constriction of their orifices. This results in dilatation of the capillaries within the myocardium, with stasis and anoxia. Prior and Wyatt[29] were impressed by the changes within the papillary muscles, and they suggest that degenerative processes in these muscles may facilitate the production of ventricular failure. Several authors have also commented on the splinting action of the thickened endocardium which may limit the expansion and contraction of the ventricle, as in constrictive pericarditis, and thus initiate heart failure. No doubt all of these factors, either alone or in combination, are operative.

Collagen Disease: Hill and Reilly[16] reported a case of a two months old Negro girl in whom the endocardium throughout was thickened. All valves were stenosed and showed an enlarged, myxomatous nodular appearance. Special stains of these valves showed fibrinoid degeneration

which was interpreted as being characteristic of collagen disease. The authors concluded that the evidence strongly suggests that endocardial fibroelastosis belongs to the collagen disease group. In considering this suggestion it should be observed that similar changes have not been reported by other observers. Moreover, inflammatory exudates in the endocardium and myocardium are generally not present, and the widespread changes usually noted in collagen disease also are uniformly absent.

Anoxia: Johnson[18] has contributed a stimulating hypothesis based on his study of twenty-three hearts with endocardial fibroelastosis occurring among 210 congenitally malformed hearts. All of these twenty-three hearts revealed developmental anomalies capable of producing anoxia. These usually involved: 1) an anomaly of the coronary arteries in consequence of which unoxygenated blood was delivered to the endocardium; 2) premature closure of the foramen ovale which prevented oxygenated blood from entering the left atrium and ventricle; or 3) valvular atresia in which stagnation anoxia developed. On the basis of this evidence Johnson advanced the hypothesis that at least one factor in the development of congenital endocardial fibroelastosis is endocardial anoxia. This hypothesis may be helpful in explaining some cases of the disease, but it cannot be applied to the great number of the reported cases in which the only abnormality is endocardial thickening.

Differentiation of Bulbus Cordis: Dennis and associates[8] have advanced a theory for the pathogenesis of endocardial fibroelastosis based on the differentiation of the bulbus cordis. This is incorporated into the ventricles in early embryonic life, dividing into right and left parts. The right bulbus becomes part of the right ventricle and infundibulum, while the left normally atrophies, and disappears. Dennis quotes Keith as stating that the bulbus behaves in the developing heart "exactly as does the granulation tissue of a healing wound." This has suggested to these workers that left-sided endocardial fibroelastosis results when there is proliferation and overgrowth of the proliferating endocardium of the left bulbus cordis. Organization and contraction of this tissue could result in a thickened endocardium, obstruct the thebesian vessels, and produce distortion of the valves. Changes in the right heart could follow overgrowth of the lining of the right bulbus. This hypothesis is a novel one, but it is as yet not supported by any available objective proof.

Endocardial Fibroelastosis and Coarctation of the Aorta: Oppen-

heimer[28] reviewed the problem of adult-type coarctation of the aorta in association with endocardial fibroelastosis in infancy. She found fourteen cases in the literature of adult type coarctation of the aorta in children under two years of age. In six of these cases fibroelastosis of the endocardium was present, and in three of these six it was given as the cause of death. Oppenheimer described five additional cases of her own, with adult type coarctation of the aorta in children age four to twenty-three months. In four, death was associated with heart failure, and all of these had severe endocardial fibroelastosis. The fifth patient died of pneumonia without heart failure, and coarctation was an incidental finding at autopsy; fibroelastosis was not present. Oppenheimer also collected a control group consisting of eleven cases of coarctation of the adult type in older children and adults, ranging in age from seven years to fifty-eight years. All of these patients had symptoms of coarctation and hypertension. Seven died following surgery, and four died from a ruptured cerebral aneurysm. None of these hearts showed endocardial fibroelastosis. From these studies Oppenheimer concluded that the association of endocardial fibroelastosis in four of her own five cases and in six of the fourteen cases of coarctation in patients under two years of age previously reported in the literature, suggests that fibroelastosis, like coarctation, is an anomaly of development, and is not secondary to long-standing hypertension from coarctation of the aorta.

Abnormal Development: Several attempts have been made to explain endocardial fibroelastosis on a developmental basis. As has been indicated, Pototschnig[3] thought that the change resulted from a simple non-inflammatory hyperplasia of fibroelastic tissue. Gross[2] also accepted this explanation. More recently Tedeschi and Damodaran[31] advanced the idea that under the influence of changed environmental conditions, of obscure nature and cause, the embryonal fibroblast of the mural endocardium loses its normal organizing power, and gives rise to an excessive and unbalanced proliferation of collagen and elastic fibers, resulting in a hamartomatous type of growth. A third suggestion has been offered by Prior and Wyatt.[29] They consider the term fibroelastosis to be faulty because it implies both mural and valvular lesions that are similar in type. Instead they suggest the term endocardial dysplasia with or without valvular involvement, as a more accurate designation for the combined lesions.

General Discussion

None of the four hearts which I personally have studied showed valvular abnormalities, and I therefore cannot claim any first-hand knowledge of this change. However, there are several histologic descriptions of involved valves in the literature, and among these are the following: 1) Elastic tissue is scanty or completely absent. 2) The deformed cusps retain their normal basic architecture. 3) There is an increase in basophilic ground substance. 4) The resulting appearance is described as "myxoid" or "myxomatous." Because of the absence of elastic tissue in the valves, Prior and Wyatt[29] suspected the valvular process to be a separate though related anomaly. But as has already been indicated in a previous section, the luminal portion of the thickened endocardium frequently reveals changes identical with those described in affected valves, namely, absence of elastic fibers, swelling, edema, increase in ground substance, and a myxoid appearance. For this reason it appears probable that the valvular changes and the endocardial changes are qualitatively similar, but differ only in the quantitative amounts of elastic fibers and collagen which are present. If this suggestion has validity, then a more precise morphologic designation for the disease should be "endocardial fibro-myxo-elastosis." Such an appellation would embrace not only the endocardial alterations, but the valvular changes as well.

The observed changes in the coronary and other arteries have several implications. They suggest first, that the endocardial lesions in the disease under discussion may in fact represent the end-result of a primary alteration in the cardiac arterial tree. Further, the finding of arterial changes in organs other than the heart indicates that endocardial fibroelastosis is a generalized arterial disease, and not, as has long been considered, a disease with manifestations limited to the heart. We now have a morphologic basis for the protracted diarrhea in the infant reported as Case 1 by Collier and Rosahn.[7] This child, which at autopsy (No. 50-39) showed the classical findings of endocardial fibroelastosis, had persistent and unexplained diarrhea. Sections of the small bowel, routinely stained at the time with hematoxylin and eosin, failed to disclose any significant lesions. Subsequently these same tissues were restained with elastic tissue techniques which revealed extensive periarterial hyperelastosis (Fig. 5) in the medium-sized mesenteric arteries, a lesion which was not known to exist at the time of the original report. A third thought suggested by

these findings is the possibility of a diagnostic procedure. If the disease is characterized by generalized vascular changes of a particular type, then perhaps the small arteries in a muscle biopsy may reveal these changes and lead to the diagnosis. This procedure has not been employed as yet because of our limited experience with these cases, but it is offered here as a possible diagnostic aid.

Certain facts about this disease are clear and undisputed. Most of the affected children die of heart failure, and the mechanism of heart failure is related to the icy coating over the endocardium. Why this coating develops is still the subject of much speculation. Most modern workers agree that the concept of fetal endocarditis is no longer tenable, and that the disease is a basic developmental anomaly. In a consideration of the mechanism of production of developmental abnormalities, it is important to differentiate between two different processes. The first is a true aberration in the germ plasm, an alteration in the genetic constitution which results in an abnormality in the developing fetus. The second is actually the result of an external, i.e., environmental, influence on the fetus, which has been developing normally until the time of exposure to the environmental change. Such an environmental factor may perhaps result from an altered maternal state due to nutritional, hormonal, infectious or other impacts. In reviewing the pathogenesis of the disease, the evidence accumulated to date strongly suggests that the first of these two mechanisms is operative, namely, that the aberration in development results from a true genetic determinant.

This hypothesis is based on three fragments of evidence from as many different laboratories. Ullrich[38] in 1938 published a detailed report on each member of a group of male triplets. The thirty-seven year old father and the thirty-five year old mother were not related. The first two infants were identical twins with a common placenta and a single amniotic sac. The third had a separate placenta and sac and was non-identical. Within six weeks of each other, at ages eight months and nine months, the identical twins died with characteristic symptoms and signs, and autopsy findings, of endocardial fibroelastosis. The third dissimilar member of the trio had a heart of normal size by roentgenogram, gained weight, and had no cardiac symptoms.

In 1943 Weinberg and Himelfarb[4] published the case reports of two siblings, a girl and a boy, the second and third children in the family. The first of these sibs died at age four and a half months, and

the second sib died at three and a half months. Both showed the characteristic clinical signs and autopsy evidence of endocardial fibroelastosis.

The third piece of evidence has not previously been published, and permission to record it here has been generously granted by Dr. John M. Craig,[39] Associate Pathologist to the Children's Medical Center, Boston. In the records of that institution is an authenticated occurrence of endocardial fibroelastosis, demonstrated at autopsy, in each of two children, the issue of the same parents. The case reports, provided by Dr. Craig, and published with his permission, follow:

Case Reports of Occurrence of Endocardial Fibroelastosis in Two Sibs: (Information about the first case was obtained from the Armed Forces Institute of Pathology.) The first sibling was a four months old female infant who was admitted on June 9, 1943 and died the next day. Since birth the baby had been suffering from attacks of vomiting. On the second day of life she had a cyanotic attack. When about two months old the vomiting became less persistent. On June 6 the baby refused its bottle and regurgitated what it did take. This continued until June 8 when the child began to vomit persistently; at the same time she had a temperature of 103°F. rectally. On the day of admission, cyanosis of the lips and nail beds was noted, and marked dyspnea developed. On admission the child was moribund, and had marked dyspnea and cyanosis. There was a respiratory grunt. The heart rate was too rapid to count. No abnormalities were detected in either lung field. The liver was palpated 5 cm. below the costal margin. Chest roentgenogram revealed suggestive cardiac enlargement. The white blood cell count was 10,500 per c.mm. with 80 per cent neutrophiles. The CO_2 combining power was 29 vols. per cent on admission. Hypodermoclyses and O_2 were administered, but the child expired six hours after admission.

At autopsy the heart was markedly enlarged and dilated, weighing 60 Gm. The epicardial surface was smooth. There were a small number of tiny petechial hemorrhages on the posterior surface of the right auricle. The large vessels at the root of the heart were normally arranged, and although a ductus arteriosus could be demonstrated, it was not patent. There was a striking thickening and creamy opacity of the endocardium of the left ventricle, which was more prominent over the septum than elsewhere. On the right side of the heart the endocardium was smooth, translucent and glistening, and the red color of the underlying muscle was clearly discernible. The valve leaflets were all well-formed, with thin translucent freely pliable leaflets. The chordae tendineae were delicate and threadlike. The aorta and coronary vessels were thin-walled and elastic throughout.

The second sibling was a four and a half years old boy who was known to have had a systolic murmur at the age of two years. He had been active and had grown well until four months before his death. Then he developed an upper respiratory infection, with rhinorrhea and a dry cough. A week before admission he became listless and pallid. Three days before admission he became anorexic and vomited; his respirations became rapid and shallow, and he was found to have a gallop rhythm. On admission his neck veins were distended, the heart was enlarged beyond the mid-clavicular line, the cardiac rate was 148, a gallop rhythm was present. Rales were heard at both lung

bases, and the liver was palpable 6.0 cm. below the costal margin. Cyanosis of the lips and edema of the ankles were present. On admission the urine contained albumen 1 plus; the hemoglobin level was 13.0 Gm. The sedimentation rate was normal, the blood leukocytes were normal in number and distribution, and the non-protein-nitrogen was 51 mgm./100 cc. A chest roentgenogram showed an enlarged heart with a prominence of the "left waist" and a small aorta. Electrocardiograms showed a left ventricular preponderance. He was given a course of ACTH without benefit but gradually responded to digitalis with a return to compensation of heart function. After a stay of two weeks, he was transferred to the House of the Good Samaritan for a four-week period. At discharge, he still had an enlarged heart. At home, he was continued on digitoxin. Three days before his final admission, two and a half weeks before death, he became more listless, pale, dyspneic and orthopneic. His neck veins enlarged and his liver became more easily palpable. On his last admission, he was as noted before. He was showing gradual improvement until the day before death when he became acutely ill, developed signs of pneumonia, a high fever and a leukocytosis of 25,000 with 91 per cent polymorphonuclear cells in the smear of the peripheral blood. He rapidly became comatose with a shock-like state and died on the thirteenth hospital day.

At autopsy, the heart was grossly enlarged, the cardio-thoracic diameter being 11.5/19.0 cm., the left ventricle and right auricle being the most dilated of the heart chambers. The left ventricle had an almost uniformly thickened, opaque and shiny endocardial surface. This involved the complicated trabecular pattern near the apex and penetrated deeply into the myocardial substance. No fibrosis or infarction of the subendocardial muscle layers was found. The cusps of the mitral valve were thickened especially near the junction of the posterior and anterior cusps. The valve was not stenotic but may have been insufficient due to the shortened condition of the cusps. The aortic valve was slightly thickened and was bicuspid in character. No stenosis or insufficiency of this valve was found. The right lung was firm and noncrepitant throughout. Microscopically it displayed an intense congestion, marked pulmonary edema and a widespread early pneumonia. In the left lung, the inflammatory reaction was less widespread, but the congestive and edematous features were still present. In the lower lobes, extensive aspiration of stomach content was found in the smallest bronchioles and respiratory alveoli. The spleen was slightly enlarged and was both congested and displayed the features of a toxic reaction. The liver, while not enlarged, displayed a curious congestion of the mid-lobular areas. No passive congestion was present in the central areas where it is usually encountered. The left kidney was small weighing but 26 gm. against a weight of 70 gm. for the right. Microscopically, no evidence of old pyelonephritis or glomerulonephritis was found. The presence of a small cartilage rest gives support to the belief that this kidney was a congenitally hypoplastic one. The lymph nodes of the hilar regions showed a mild early acute lymphadenitis in addition to their diffuse congestion. The culture of the lungs' and heart's blood was negative. A small area of ulceration was seen grossly in the stomach, microscopically this had the character of Cushing-Rokitansky ulcers seen in intracranial disease. No evidence of myocarditis was present in the heart. A few collections of lymphocytes were seen in the epicardium but these were not considered significant as far as the fundamental nature of the illness was concerned. The cause of death must be attributed to heart failure secondary to the structural anomaly of the heart wall. Of considerable interest in this case is the occurrence of almost identical lesions in a sibling of this infant.

Proof of the hereditary determination of human attributes is extremely difficult, except when the attributes have widespread distribution, as for example, the Rh factor. When the attribute occurs infrequently and sporadically, as does endocardial fibroelastosis, ultimate verification of its hereditary nature must depend on the slow and painstaking accumulation of recorded cases, associated with detailed study of the family histories of affected individuals. No such final proof of the hereditary nature of endocardial fibroelastosis is available. However, this disease occurs so infrequently that its development in each member of two different pairs of siblings, and in identical twins of a group of triplets, the third dissimilar member of which was normal, appears to be well outside the realm of chance or random sampling. It is on the basis of this evidence that the genetic nature of endocardial fibroelastosis is hypothesized. If the disease is in fact hereditary, it is probably transmitted through a recessive gene. According to Fraser,[40] a rare recessive inherited disease will be characterized by the fact that the affected person will nearly always have unaffected parents. Also, because of the small size of human families, a majority of cases will appear "sporadically." The distribution and occurrence of endocardial fibroelastosis appear to fulfil these characteristics.

Conclusions

Three general concepts have emerged from this study of endocardial fibroelastosis:

1. Morphologically, the endocardial changes are those of a fibromyxo-elastosis; the valve changes are qualitatively similar to the endocardial changes, differing only in the quantitative amounts of collagen and elastic tissue present.

2. In addition to the endocardial lesions, small and medium-sized arteries also show abnormalities. There is a periarterial hyperelastosis in the heart, and also in other parenchymatous organs. The changes are therefore generalized and systemic, and not limited to the heart alone.

3. Evidence is presented which suggests that the disease is genetic in origin.

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DISCUSSION

JANET S. BALDWIN: It has been a great pleasure to hear such a splendid review of the subject as Dr. Rosahn has given. In view of what he has said about the course and mortality you can see that the clinician often finds the condition extremely difficult to diagnose ante mortem as there are very few specific signs and at least 30 per cent of the young infants who die of the disease have the acute fulminating type and appear in the hospital desperately ill. The type of patient who makes one suspect endocardial fibroelastosis is a baby who probably has a history of only short antecedent difficulty, whose most prominent symptom is dyspnea, with no evidence of cyanosis except terminally. In cases with involvement of valve areas, murmurs may be present. In many instances, however, murmurs are not heard or are of poorly localized types which are relatively soft. The heart sounds may be of rather poor quality, a non-specific finding. If the baby is not too sick, so that fluoroscopic or roentgenographic examination can be made, a large globular heart with no characteristic outline is found. The electrocardiogram is probably the greatest help we have clinically. From the fact that the involvement in most cases is predominantly of the left ventricle, the hypertrophy of this chamber will result in left axis deviation. This finding is a very helpful clinical guide in narrowing down diagnostic possibilities. Under the age of six months the normal pattern is that of right axis deviation with more predominance of the right ventricle in precordial leads than is seen in older patients.

There are other possibilities that must be considered in a non-cyanotic infant who presents little or nothing in the way of murmurs and a large heart on roentgenologic examination. The condition first to be differentiated from endocardial fibroelastosis is the anomalous origin of the left coronary artery from the pulmonary artery. That condition also will give difficulty predominantly affecting the left side of the heart. The question is still unsettled as to whether the inadequacy of this circulation from the pulmonary artery is due to low oxygen saturation of the blood from this source, or whether the lower pressure of the pulmonary artery cannot pump the blood through with adequate force to create good circulation. But be that as it may, the myocardium

supplied by this left coronary is jeopardized and the left ventricle becomes markedly dilated. The electrocardiogram has a pattern similar to that of myocardial infarction with notable inversion of the T waves. These differential points of electrocardiographic evidence of coronary insufficiency alone as against the pattern of left ventricular hypertrophy may help the clinician to make a postulate as to which of the two types of conditions discussed may be present. It has been considered that attempts at diagnosis were impossible on clinical findings but with more extensive application of electrocardiography there are more cases correctly diagnosed clinically and confirmed at autopsy. Cases with anomalous origin of the left coronary artery but rarely show any definitive murmurs.

A few other conditions may have to be considered in a non-cyanotic baby with a big heart and no murmurs. In infancy occasionally coarctation of the aorta will cause marked increase in the size of the heart. High blood pressure in the upper extremities with low or unobtainable blood pressure in the legs is the clinical clue to this condition. Other rarer conditions are rhabdomyoma and glycogen storage disease of the heart. Beriberi and the African disease, kwashiorkor, are added more for academic interest than as clinical possibilities in pediatric cardiac practice in our geographic area.

From the point of view of clinical differentiation I will show some instances that point out how similar in many ways two cases may be. This first slide shows the pathology of a case of endocardial fibroelastosis with the coating, which is not as pretty as in Dr. Rosahn's colored photographs, but you can see here the marked thickening of the endocardial layer. This child came to postmortem examination in the first few months of life after a brief illness, with acute dyspnea and a large dilated heart. The next slide shows the roentgenogram, and you can see there is rather a nonspecific type of big heart, and the barium swallow shows evidence of left auricular enlargement. This latter finding is now being considered as of diagnostic help. The last slide in this particular case is of the electrocardiogram, which shows the pattern of much more of left ventricular than of right ventricular dominance.

In contrast the next slides show the findings in an infant of almost the same age, the first case in whom autopsy confirmed the presence of a left coronary artery arising from the pulmonary artery. Here again was a child apparently perfectly normal up to a short time before coming into the hospital with severe dyspnea and who was found to have a very big heart, no murmurs, and who died within two weeks. In this instance the slide of her roentgenogram shows a heart of greatly increased size. The most help towards the postulated diagnosis was obtained from this electrocardiogram showing the inversion of T waves in the standard leads.

Such special diagnostic tests as cardiac catheterization and/or angiocardiography are always considered in a difficult cardiac case. Venous cardiac catheterization by which the right side of the heart is studied could not give any information of value in the types of conditions we have been considering. Except for confirming the presence of coarctation of the aorta, which is suspected because of abnormal blood pressure relationships, the injection of radiopaque dye with current techniques will not help in differential diagnosis. Further developments in more rapid angiocardiography may hold some diagnostic promise. In many instances the course of the illness is so brief and the infant so sick that even standard procedures may not be fully carried out.

Some of the babies with these conditions are amongst those who are found dead in bed although a high percentage die quickly, within two weeks. Certainly all forms of appropriate therapy, such as oxygen treatment of congestive failure with administration of digitalis products and mercurials, should be tried. Some of the cases of presumptive endocardial fibroelastosis may be of the more chronic type and can be carried through episodes of acute difficulty from failure precipitated by respiratory infection.

Obviously fibroelastosis is a very discouraging disease for the clinician as there is so little that can be done in the vast majority of cases once it has been diagnosed.

It is of utmost importance to make every effort to carry out all diagnostic approaches and arrive at as exact a diagnosis as possible particularly to prevent missing the recognition of such congenital anomalies as can be helped by surgery, such as coarctation of the aorta. Correction of this condition at a very early age has been successful in some children in intractable failure who obviously would have died had surgery been delayed. Cases with valvular pulmonary stenosis and no associated blood shunts should always be kept in mind. In such cases the heart may become very large but in contrast to conditions previously considered the murmur is prominent and the electrocardiogram shows obvious right axis deviation.

I do not think there is anything more from the clinical aspect of endocardial fibroelastosis that Dr. Rosahn has not touched on, except for noting the increasing incidence. The fact that case reports are increasing makes one wonder if this is an actual increase of the disease or of its recognition.

PETER GRUENWALD: In thinking about the way these babies died, I think one should consider the possibility that they may not all die in heart failure. Dr. Baldwin has mentioned that some of them had a cold which preceded death. We know that a number of other babies who do not have cardiac malformations die in a similar way, and we often find a mononuclear pneumonia of which we do not know the real significance or cause, and which is often preceded by a cold. I think that in many of these cases in which there have been no signs of decompensation, the rapid death has been due to the combination of the mysterious pneumonia with heart disease, or due to heart failure precipitated by such a pneumonia.

JACOB TAUB: I have seen three such cases and I would like to confirm what Dr. Rosahn has said. All three patients were found dead in bed. In one case the father stated that he had had an infant daughter who had died of a "tumor" of the heart. This would support a theory of congenital aberration. An interesting finding in two of the cases was marked hypertrophy of the thymus. I wonder if in any of Dr. Rosahn's cases, or in those he encountered in the literature, any similar enlargement was noted.

PAUL D. ROSAHN: It has been suggested that many of these patients die as a result of pneumonia rather than from heart failure, and I think that this is an accurate observation. Many of the case reports indicate that affected children had no untoward symptoms until an infection of the upper respiratory tract precipitated admission to the hospital where examination revealed both pulmonary infection and heart failure. Whether death results from the upper respiratory infection or the heart abnormality is not easy to determine. The combination of both conditions is probably responsible for death.

I do not have any personal experience with hyperplasia of the thymus in this condition, but it is my suggestion that perhaps the cases in which the thymus appeared to be hypertrophied were those with a very short clinical course, where death occurred within a matter of hours; in other words, it is possible that the observed hyperplasia of the thymus may not in fact have been hyperplasia. The large thymus may have been of normal size in an individual who died suddenly, before atrophic changes could occur.

I want to thank the Society for the privilege of coming here to tell you about this work, and to thank Dr. Baldwin for a very interesting discussion.

Cardiac Hypertrophy and Insufficiency of Unknown Etiology

ABSTRACT OF PAPER AND DISCUSSION

SAMUEL K. ELSTER,* LESTER R. TUCHMAN and HENRY HORN

The Departments of Medicine and Pathology, The Mount Sinai Hospital

There is a clinical entity of cardiomegaly and intractable congestive heart failure not related to the usual causes of cardiac enlargement, such as hypertension, coronary arteriosclerosis, rheumatic fever, congenital defects, syphilis, glycogen disease, amyloidosis or diffuse vascular disease. This group has been variously designated as idiopathic cardiac hypertrophy, cardiac hypertrophy of unknown cause, fibrosis of the endocardium with mural thrombosis, endocardial fibrosis, etc. In the past fifteen years at The Mount Sinai Hospital ten such cases have come to necropsy. The present report deals with the clinical and anatomic pattern of these cases.

Seven males and three females from the ages of twenty-four to fifty-three make up this series. No dietary factors could be incriminated. The clinical courses were brief and were marked by severe congestive heart failure. Pulmonary infarction occurred in six patients. The physical findings were those of cardiomegaly with left and right-sided cardiac insufficiency. Major abnormalities of cardiac rhythm occurred in three patients and in four patients grade IV systolic murmurs were heard. A low systolic, slightly elevated diastolic blood pressure, with diminished pulse pressure, was common, but in none was there evidence of hypertensive cardiovascular disease. The temperature was intermittently elevated in many instances. The laboratory tests failed to yield any clue as to etiology. Leukocytosis was present in four and late azotemia in four. Special tests such as LE cell phenomenon, serum protein bound iodine, blood cultures, skin and muscle biopsies and congo-red retention tests were negative. Only the most transient response to the usual therapeutic measures for congestive heart failure was obtained. Anticoagulants, cortisone and vitamins failed to impede the progression. The course was rapid and terminated fatally. Eight patients succumbed within eighteen months following the onset of symptoms.

Pathologically, the hearts showed uniform hypertrophy and dilatation. They varied in weight from 430 to 800 grams. The pericardium was normal, except that petechial hemorrhages occurred in three, and minor fibrous adhesions in two. A small amount of pericardial fluid was present in six. The heart valves were normal, except for minimal thickening of the mitral valve in one case and the tricuspid and pulmonic valves in another. The coronary arteries were patent throughout with but minimal atherosclerosis in six. In one of these, there was a fresh occlusion of a secondary branch of an accessory right coronary artery in the wall of the right ventricle. This was not considered to be causally related to the cardiopathy. Minimal arteriosclerosis of the aortae and the pulmonary arteries was noted in many. Mural thrombi were found in the chambers of seven hearts. In three, these were confined to the left ventricle, whereas in the remainder, multiple chamber involvement was present. Seven instances of pulmonary infarction and four of systemic infarction of kidneys and spleen occurred.

Histologically, the predominant lesion was that of uniform myocardial hypertrophy. In addition, there were secondary degenerative and necrotic muscular changes, principally in the endocardial and subendocardial areas. The earliest lesions comprised myofibrillar degeneration, loss of nuclei and smudging of sarcoplasm. Later, a chronic inflammatory reaction with lymphocytes, mononuclear cells, occasionally polymorphonuclear leu-

* By invitation.

kocytes and plasma cells appeared. Fibroblasts and capillaries invaded the areas and subsequently fibrosis occurred. The most advanced lesions were those of avascular and acellular scars. These lesions were focal, but widely distributed in the inner aspects of the myocardium. Thickening of the endocardium was common and was often confluent with the myocardial scars. The thrombi were in varying stages of organization and often overlay areas of fibrosis and inflammatory reaction. There was no evidence of renal or systemic arteriolar sclerosis.

A review of previously described similar cases has failed to afford a known etiology. None of the causes heretofore suggested as primarily responsible for this syndrome is believed to have been established. Vitamin or nutritional deficiency, primary myocarditis, endocardial fibroelastosis, primary endocardial fibrosis or "collagen disease" do not appear to be the causative factors. It is suggested that myocardial hypertrophy of completely unknown etiology is the initiating mechanism, and that myocardial anoxia, a concomitant of the considerable hypertrophy and dilatation, is an important factor in the development of the secondary degenerative myocardial changes. These then intensify the cardiac abnormality and result in increased myocardial failure.

DISCUSSION

DICKINSON W. RICHARDS, JR.: I appreciate the opportunity to discuss this interesting and extremely well presented paper. I think I should first clear up a little misunderstanding which I found from conversation this evening: the report has gone around that our group at Bellevue, Drs. Ferrer, Harvey and Fishman, have worked out the hemodynamics of this intriguing and rare condition. That is somewhat of an overstatement. Actually one case has been studied, and I think I will have to tell you about the sad case of Lum Kai, sad for him, and sad for us. He was a middle-aged Chinese who was followed for a number of months, a case quite characteristic of this condition clinically. He was studied by catheterization toward the end of his course, while he was recovering, before he had quite recovered compensation, and then he got better and was discharged. As he traveled from Bellevue down to Chinatown on his way home, he was set upon and murdered, and so Lum Kai came back to Bellevue. His lethal injuries were thoroughly investigated, but unfortunately the heart was not examined. So our physiologic data are perhaps on just as tenuous ground as other physiologic data usually are; but if Lum Kai's cardiac status is what we think it was, our studies showed that he had a hypodynamic heart, a low cardiac output, with pressures not greatly different from normal, a slightly elevated pressure such as one gets in the pulmonary circuit of an individual recovering from congestive failure. That perhaps does let us infer that these cases are those with low outputs, hypodynamic hearts; they are not of the type of beriberi heart disease, or any of our cases of chronic alcoholism, hyperthyroidism, anemia, and the rest, all of which tend to give elevated cardiac outputs in the state of failure. Thus these cases of idiopathic cardiac hypertrophy would appear not to belong in any nutritional deficiency group. As has been said, cardiac catheterization generally does not help us very much. Through the courtesy of Drs. Kuschner and Weiss, I was able to look over the clinical and pathologic findings in six other cases which Dr. Weiss has collected recently from the material at Bellevue, and they seemed to confirm the criteria of idiopathic hypertrophy of the heart. They were very carefully chosen and such situations as arterial hypertension and other conditions that might have confused the issue were rather carefully ruled out. I think there is not very much additional that should be said about this group of cases. They conformed fairly well to those which Dr. Elster has so well described. I might say that only one of ours showed any significant evidence of fibrosis, and again it was endocardial fibrosis. Some of the others, especially those running a more fulminating course, did not have any of this, but chiefly hypertrophied cardiac muscle. I wonder whether Dr. Elster will comment on the question of whether these cases all represent one disease or whether there is

perhaps more than one entity in the group, and whether the cases in which there is a lot of fibrosis are idiopathic hypertrophy, or a later event in the same general category. I have nothing to offer either one way or the other. In our one case of endocardial fibrosis there apparently had been a history of heart disease for a matter of years.

I have just one other comment to make that may be some help diagnostically in the use of cardiac catheterization in these studies; it is not altogether theoretical. As you know, the pathognomonic, or almost pathognomonic sign of chronic constrictive pericarditis or chronic cardiac encasement is the form of the right ventricular pressure curve. If this is a normal curve (shown in drawing on board) you will note a small auricular systole, then right ventricular systole, and in diastole the pressure curve drops sharply below the zero line as the tricuspid valve opens and blood begins to go in and systole is repeated. In the case of constrictive pericarditis the systolic pressure is, if anything, a little less than normal, and the characteristic feature is what is known as the diastolic dip, the pressure as the ventricle relaxes dipping far below the zero level. The cause of this dip is not completely understood. It has been suggested that the thick encasement is distorted during systole and in relaxing suddenly springs back into this position and therefore produces a sort of suction; and this, it might be said, is perhaps as good an explanation as any.

So much for pericarditis. Dr. Goyette in Denver has been studying these patients and has one who proved to have endocardial fibrosis and not pericardial fibrosis. Apparently the encasement of the endocardium can spring back in a similar way. Granting that we are measuring only the right ventricle and not the left, there must be this endocardial process in the right ventricle also if one is going to meet with this type of response. If one finds that kind of pressure curve, which is characteristic, we think it may be of some diagnostic aid.

IRVING GEORGE KROOP: At the last meeting of the Association of American Physicians on May 4, 1954, I believe Dr. Burwell of Boston presented cases of what he called diffuse myocardial fibrosis.[1] Apparently he also recorded these end-diastolic dips in the right ventricular pressure curves as demonstrated by Dr. Richards. These dips were attributed to a restrictive endocarditis in those cases. However, it is not clear whether Dr. Burwell's cases of diffuse myocardial fibrosis were the same as those presented tonight, or whether they were secondary to coronary disease. It seems to me that they are in the same group as those cases presented by Dr. Elster. I should like to ask Dr. Richards whether he knows about the physiologic studies in the patients presented by Dr. Burwell.

DICKINSON W. RICHARDS, JR.: I can only agree; I suppose one can have a thickening and restriction within the heart muscle just as one can on either side. I think the situation is quite analogous.

I should say finally that the request which Dr. Elster made for me to explain the cause of the hypertrophy of the heart muscle I shall have to decline to answer. It is a difficult question.

HENRY HORN: Dr. Richards has raised the question of the pathogenesis of myocardial fibrosis in these patients. I should like to re-emphasize our belief that such fibrosis is incident to the foci of myocardial necrosis. We do not look upon the latter as the initial alteration in this syndrome, for they do not in any way differ from those lesions observed in instances of coronary insufficiency. These alterations do not, therefore, represent any specific primary lesion, but are rather the sequelae of myocardial anoxia, the end result of cardiac hypertrophy. The basic cause for the myocardial hypertrophy we are at a loss to explain.

LESTER R. TUCHMAN: I have one observation to make which is clinical and not pathologic. Certainly in the older litera-

ture there is a predominance of this lesion in the colored race, and it may be that this is a type of response analogous to the keloid response in colored people. In our own material, which we draw from a predominantly white population, most cases are in people of the colored race, and as Dr. Elster brought out, where we measure our cases by the tens, in Africa the same thing is done by the scores and hundreds. The incidence is enormously greater there than here, and there must be some dietary or genetic factor that we have not yet identified as responsible for this type of response.

SAMUEL K. ELSTER: As to whether or not this group that we call idiopathic hypertrophy is caused by a uniform mechanism or a variety of mechanisms, we cannot state. Until we can arrive at a method of establishing the etiology, these cases will be grouped together as a syndrome, and as most syndromes are finally explained, this group will become smaller and smaller and eventually disappear.

REFERENCE

1. Burwell, C. S. and Robin, E. D. Some points in the diagnosis of myocardial fibrosis, *Trans. Assoc. Amer. Phycns.* 67:67-71, 1954.

ERRATUM

In the May 1955 number of the Bulletin, on pages 413 and 414 of the abstract entitled, *Debridement of Burn Slough by Peptidases Recovered From Clostridium Histolyticus,* the illustrations (but not the legends) should be transposed. That appearing on page 413 should appear on page 414 and vice versa. We regret this error.—Ed.

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WHAT IS AGING? — *Ludwig Kast Lecture*
Albert Lansing, Emory University School of Medicine, Atlanta, Ga.

PSYCHOLOGIC ASPECTS OF AGING
Ross A. McFarland, Harvard University

EXPERIMENTAL PROLONGATION OF THE LIFE SPAN
Clive M. McCay, Cornell University, Ithaca, N. Y.

Tuesday, October 11

ARTHRITIS IN THE ELDERLY PATIENT
Joseph J. Bunim, National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland

EVALUATION AND PREPARATION OF THE PATIENT WITH DEGENERATIVE CARDIOVASCULAR DISEASE FOR MAJOR SURGERY
John S. La Due, The New York Hospital

GASTROINTESTINAL HEMORRHAGE IN ELDERLY PATIENTS
Thomas P. Almy, Cornell University Medical College

RELATION OF INCREASED LONGEVITY TO NEOPLASIA
C. P. Rhoads, Memorial Center for Cancer and Allied Diseases

Wednesday, October 12

SOME PHYSIOLOGICAL ASPECTS OF AGING — *Wesley M. Carpenter Lecture*
N. W. Shock, National Heart Institute, Bethesda, Maryland

NUTRITIONAL PROBLEMS OF ADVANCING AGE
Fredrick J. Stare, Harvard University

FLUID AND ELECTROLYTE PROBLEMS IN SURGERY OF THE AGED
Henry T. Randall, Memorial Center for Cancer and Allied Diseases

Thursday, October 13

PANEL MEETING — CEREBROVASCULAR DISEASE WITH AGING
Chairman: Irving S. Wright, Cornell University Medical College

Friday, October 14

PANEL MEETING — PROBLEMS OF RETIREMENT
Chairman: Howard Reid Craig, Director, The New York Academy of Medicine

(Continued on next page)

Second Week

Monday, October 17

THE NATURE OF THE RESPONSE TO STRESS WITH AGING — *Harlow Brooks Lecture*
To be announced

THE EFFECT OF AGING ON THE MYOCARDIUM
William Dock, State University of New York College of Medicine at New York City, Brooklyn, N. Y.

THE AGING LUNG
Dickinson W. Richards, College of Physicians and Surgeons, Columbia University

Tuesday, October 18

MANAGEMENT OF INJURIES IN THE AGED
Robert H. Kennedy, Beekman-Downtown Hospital, New York

MANAGEMENT OF SURGICAL EMERGENCIES IN THE AGED
Condict W. Cutler, Jr., Goldwater Memorial Hospital, New York

SURGERY OF CHRONIC DISEASES IN THE AGED
Frank Glenn, The New York Hospital

ANESTHESIA IN THE AGED
Emanuel M. Papper, Presbyterian Hospital

Wednesday, October 19

EMOTIONAL AND PSYCHIATRIC PROBLEMS OF AGING
Francis J. Braceland, The Institute of Living, Hartford, Conn.

NEUROSURGICAL TREATMENT OF PARKINSONISM
Irving S. Cooper, New York University-Bellevue Medical Center

REHABILITATION IN THE AGED
Howard A. Rusk, New York University-Bellevue Medical Center

Thursday, October 20

PANEL MEETING — CLIMACTERIUM: MALE AND FEMALE (Title tentative)
Chairman: Earl T. Engle, College of Physicians and Surgeons, Columbia University

Friday, October 21

PANEL MEETING — DISORDERS OF THE SPECIAL SENSE ORGANS ASSOCIATED WITH AGING: THEIR RECOGNITION AND TREATMENT
Chairman: Charles F. Wilkinson, Jr., New York University-Bellevue Medical Center

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Chairman: Henry S. Simms

Wednesday, October 12 — EVERYDAY PROBLEMS IN THE CARE OF THE AGED
Chairman: Frederic D. Zeman

Friday, October 14 — MANAGEMENT OF CARDIOVASCULAR RENAL PROBLEMS IN THE AGED
Chairman: Hugh Luckey

Second Week

Monday, October 17 — MANAGEMENT OF GENITO-URINARY PROBLEMS IN THE AGED
Chairman: Robert S. Hotchkiss

Wednesday, October 19 — PUBLIC HEALTH ASPECTS OF AGING
Chairman: W. G. Smillie

Friday, October 21 — PROBLEMS OF INFECTIOUS DISEASES AND THEIR THERAPY IN THE AGED
Chairman: Perrin H. Long

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JUNE 9 "FOR DOCTORS ONLY" will not be broadcast, the week of WNYC's Opera Festival.

JUNE 16 THE EFFECTS OF TOBACCO SMOKING—(panel)—G. Jarvis Coffin, *moderator, Assistant Professor of Clinical Medicine, Columbia University, New York,* with A. Wilbur Duryee, Herbert C. Maier, Harold E. B. Pardee and Ernest L. Wynder.

JUNE 23 LIFE IS FOR LIVING—D. Ewen Cameron, *Chairman, Department of Psychiatry, McGill University, Montreal, Canada.*

JUNE 30 PREVENTIVE USE OF PSYCHOTHERAPY IN CHILDHOOD—(panel)—Lawrence S. Kubie, *moderator, Clinical Professor of Psychiatry, Yale University School of Medicine, New Haven,* with Clement B. P. Cobb, Marianne Kris, Milton I. Levine and Marian C. Putnam.

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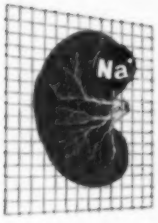

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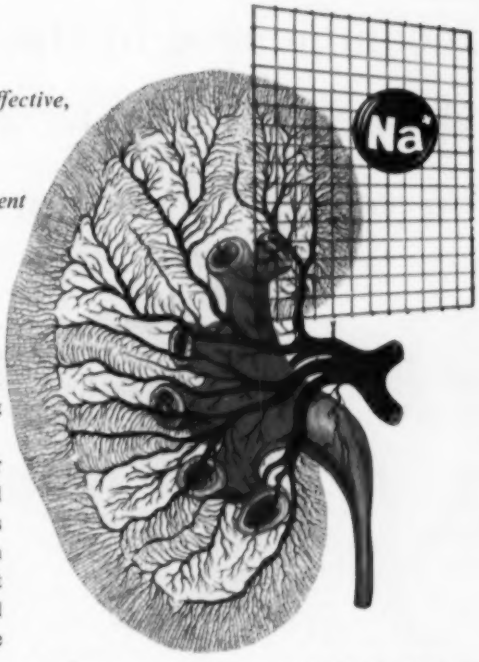

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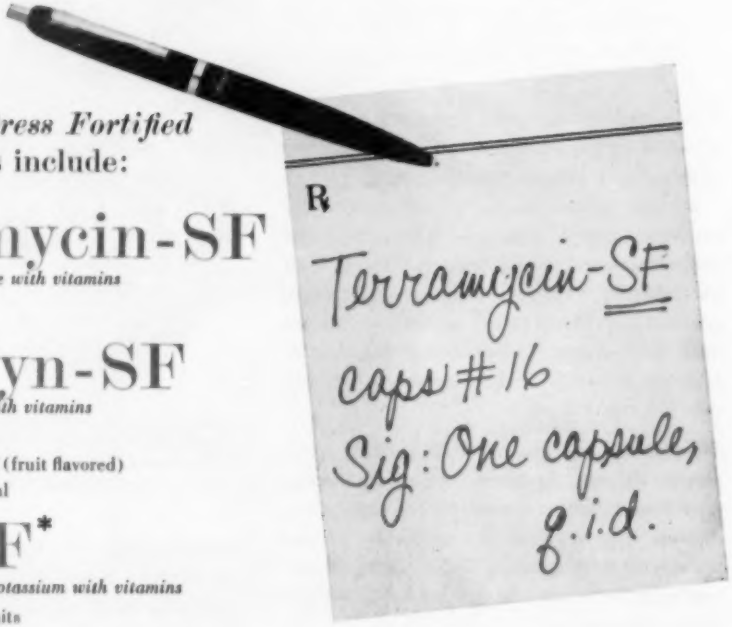

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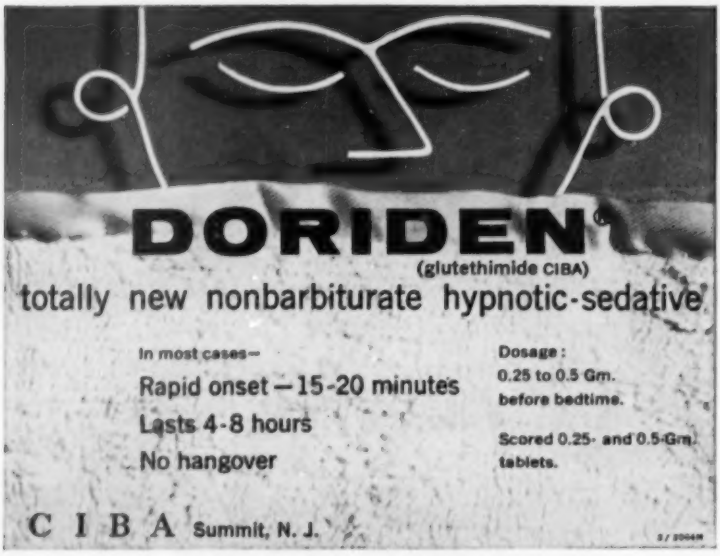

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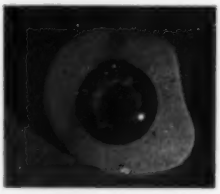

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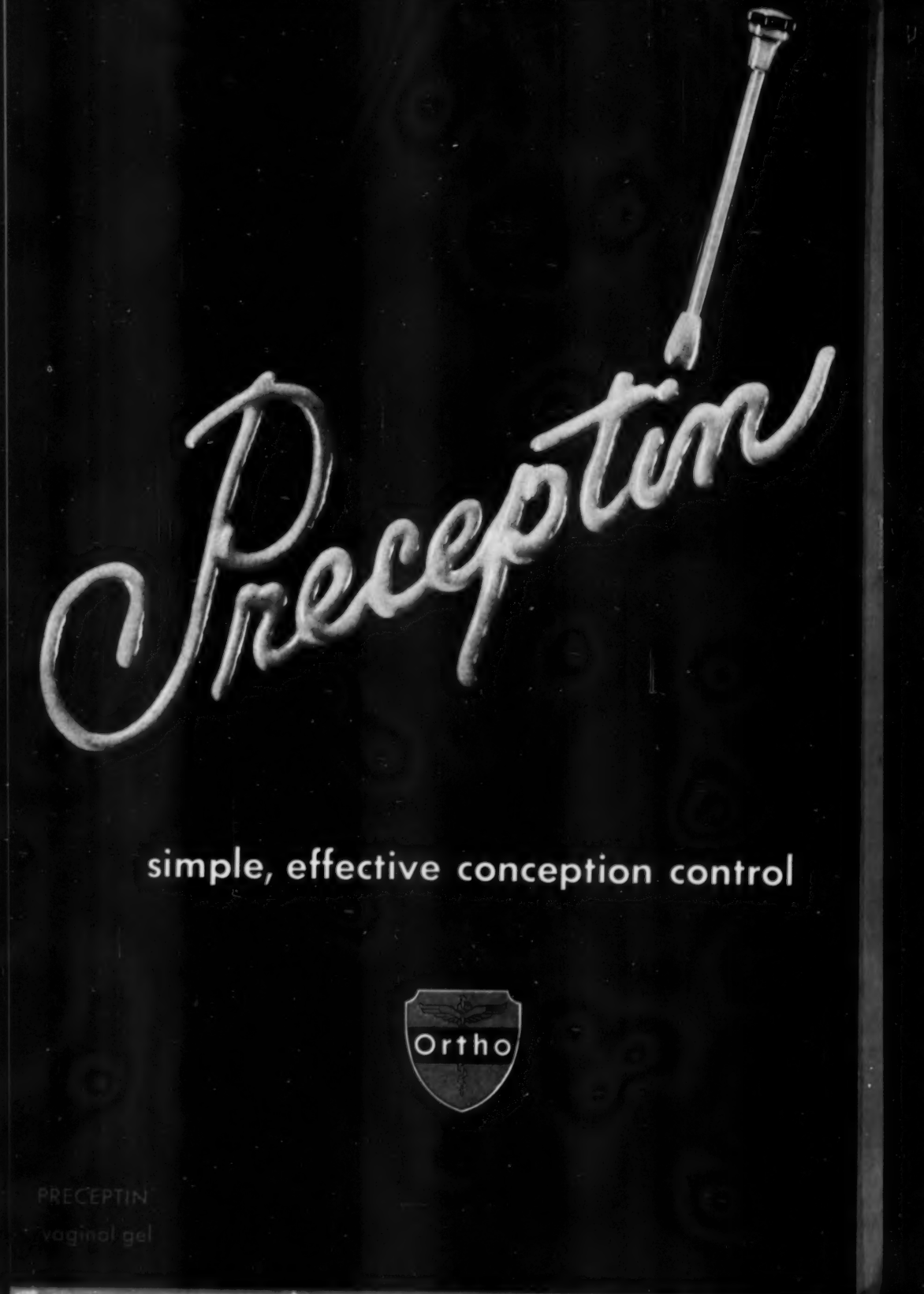
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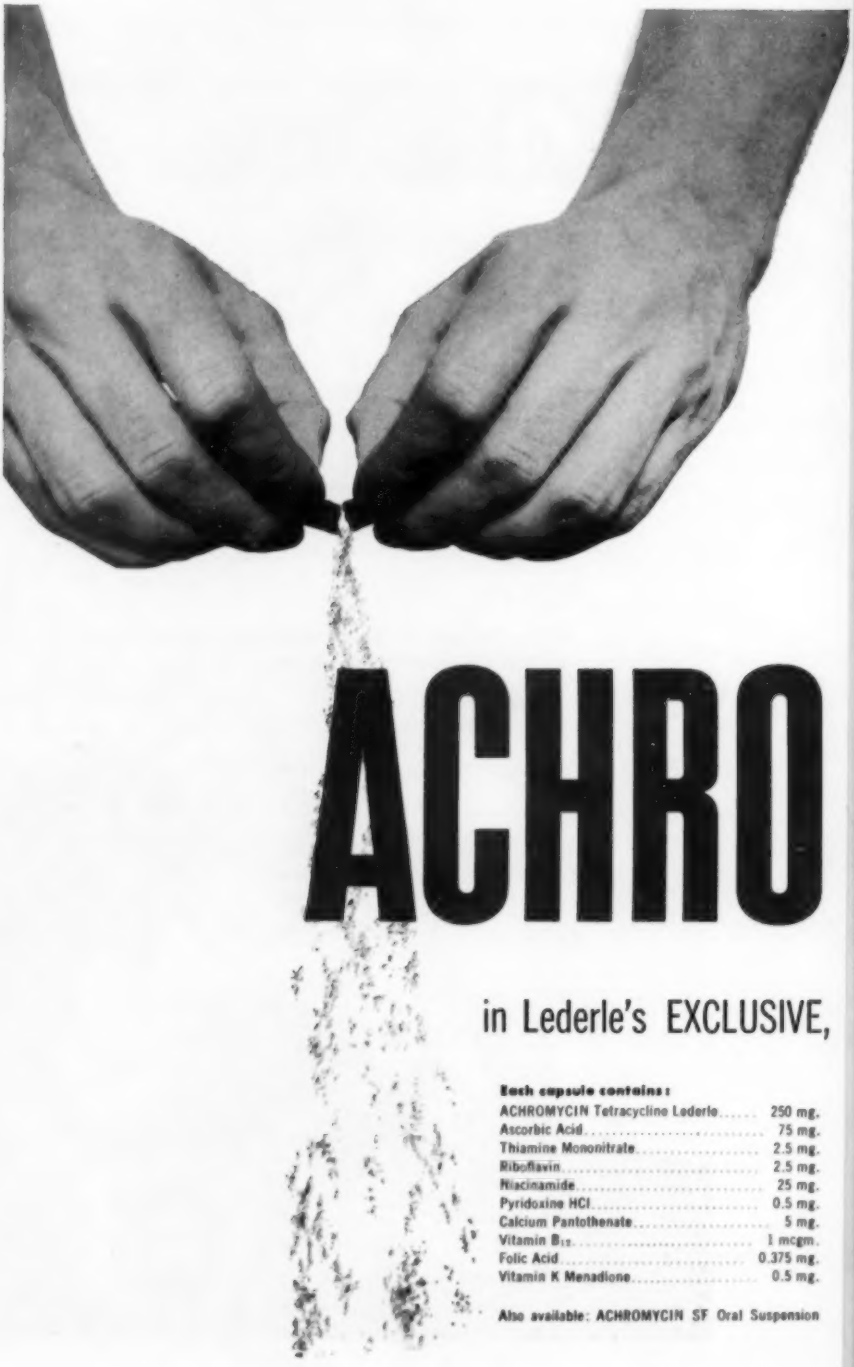

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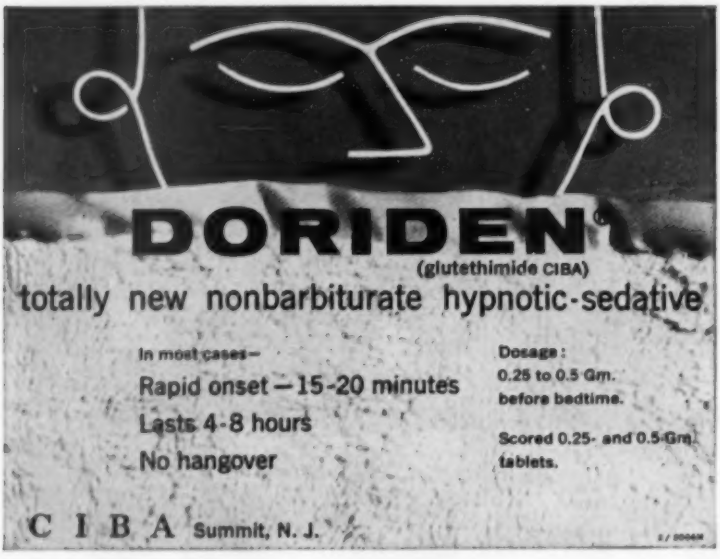

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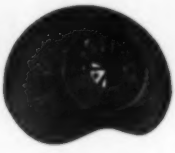

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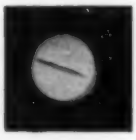

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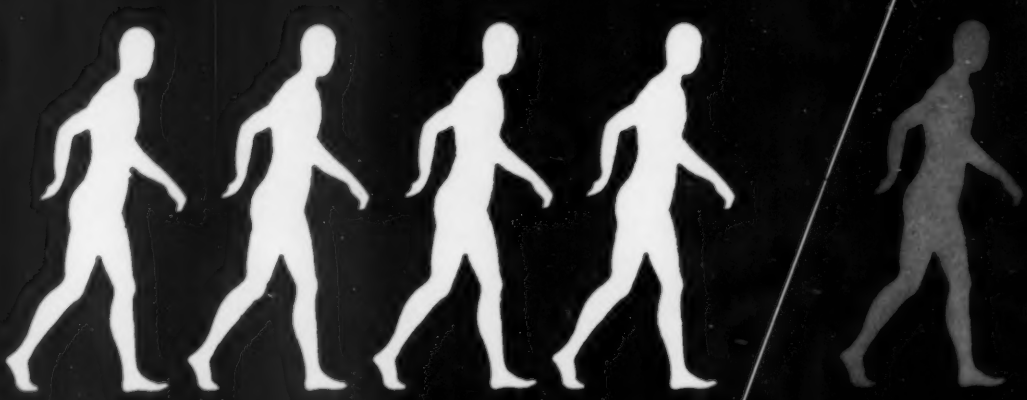

you can prevent attacks of angina pectoris

Peritrate, a long-acting coronary vasodilator, has repeatedly demonstrated its effectiveness in preventing attacks of angina pectoris in 4 out of 5 cases.[1,2,3]

Prophylaxis with Peritrate results in fewer, less severe attacks, reduced nitroglycerin dependence, improved EKG's where abnormal patterns exist and increased exercise tolerance.

Peritrate's action is similar to that of nitroglycerin but considerably more prolonged... "favorable action [can] be elicited for 5 hours or more after its administration."[4]

Usual dosage is 10 to 20 mg. *before meals* and at bedtime.

The specific needs of most patients and regimens are met with Peritrate's four dosage forms. Peritrate is available in both 10 and 20 mg. tablets; Peritrate Delayed Action (10 mg.) allows uninterrupted continuation of protection through the night. Peritrate with Phenobarbital (10 mg., with phenobarbital 15 mg.) where sedation also is required.

1. Winsor, T., Humphreys, P.: Angiology *3*:1 (Feb.) 1952.
2. Plotz, M.: N. Y. State J. Med. 52:2012 (Aug. 15) 1952.
3. Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.
4. Russek, H. I., *et al.*: Am. J. M. Sc. 229:46 (Jan.) 1955.

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(BRAND OF PENTAERYTHRITOL TETRANITRATE)

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ALL SULFONAMIDES ARE NOT ALIKE

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BONAMINE CHEWING TABLETS—the *only* motion-sickness medication which

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Well-tolerated BONAMINE is uniquely effective in a single daily dose. Notably free from side reactions.

BONAMINE medication is also indicated for the control of vertigo associated with vestibular and labyrinthine disturbances, cerebral arteriosclerosis, radiation therapy, Menière's syndrome and fenestration procedures.

BONAMINE CHEWING TABLETS contain 25 mg. of Bonamine each and are supplied in packets of 8, individually wrapped.

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